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ELECTRIC RESPONSES DERIVED FROM THE SUPERIOR CERVICAL GANGLION WITH MICRO-ELECTRODES

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(Received for publication November 8, 1939)

IT IS A WELL-KNOWN FACT that slow potentials are commonly recorded from the surface of regions made up principally of nerve-cell bodies; but the electrical activity of the single nerve-cell has remained obscured in this algebraically summated picture of temporally dispersed unit responses. The potentials recorded from the brain stem of the goldfish (Adrian and Buytendijk, 1931), the optic ganglion of the water beetle (Adrian, 1931), the mammalian spinal cord (Gasser and Graham, 1933), and the superior cervical ganglion (Bishop and Heinbecker, 1932; Eccles, 1935a) suggest two divergent views concerning the nature of the electric disturbance in the single cell—one, that it runs a slow time course corresponding to that of the summated response derived from the entire cell group; the other, that individual fast ("spike") potentials overlap in time to produce the observed smooth-contoured curve in the aggregate of many cells. The former viewpoint is supported especially by the work of Heinbecker (1936) on the median cardiac nerve of *Limulus* in which a sustained negative potential was regarded as possibly due to the activity of a single cell. On the other hand, Eccles (1936) considers the main response of the superior cervical ganglion as built up of individual cell spike potentials. Little attention has been paid to the extensive branching of both pre- and postsynaptic nerve fibers in a synaptic region. From this standpoint Bishop (1936) has criticized the analysis of Eccles, and regards the ganglionic potential as due to the activity in postsynaptic nerve fibers. Bishop furthermore laid stress on the shunting effect of surrounding tissue, a fact which may explain the smoothness of the curve recording action currents composed of spike potentials.

The micro-electrode technique seems to give valuable direct evidence of the electrical activity of the single cell. Renshaw *et al.* (1938, 1940) have recorded fast, "axon-like" potentials of 1 to 2 msec. duration from the pyramidal cell-layer in the hippocampus region of the cat. The size of the micro-electrode varied in these experiments between 30 and 80μ. The results in the present paper are obtained with essentially the same technique, but still smaller micro-electrodes have been found useful in revealing the electrical activity of single units in the superior cervical ganglion. A short preliminary report has been presented (Therman and Forbes, 1939).

METHOD

The superior cervical ganglion of cats and rabbits under light dial (Dial Ciba, 0.75 cc. per kg.) anesthesia was prepared in the usual way with care not to disturb the blood

* Fellow of the Rockefeller Foundation.

supply. By removing trachea and esophagus, which was done in most cases, the manipulation of the micro-electrode was greatly facilitated.

For standard recording of the ganglionic potential, chlorided silver wire electrodes with rubber shields were used. The inter-electrode distance was 5 to 6 mm., with the distal electrode on the postganglionic nerve trunk, usually crushed. For stimulating, the same kind of electrodes were applied to the sympathetic (preganglionic) nerve, but with greater interelectrode distance. The nerve was carefully separated from the adherent vagus nerve and cut proximal to the stimulating electrodes. Both pairs of electrodes were usually imbedded in congealing paraffine, a method which was found useful in preventing the preganglionic nerve from drying and the ganglion from moving.

Micro-electrodes were made by drawing glass capillary tubes (1.3 mm. in diameter) to a fine terminal aperture. This was done in a special machine in which the length of taper as well as the aperture could be controlled (see Renshaw *et al.*, 1940). The desired size of the opening was then obtained under the microscope by breaking off the tip of the capillary. The tube was filled with 0.9 per cent NaCl solution by suction. When using small micro-electrodes we have found the NaCl solution more satisfactory and easier to apply than a Ringer-agar solution (cf. Renshaw *et al.*, 1938). Finally a chlorided silver wire was pushed into the capillary tube as close as possible to the terminal aperture and the electrode was mounted on a micro-manipulator. The position of the micro-electrode in relation to the upper surface of the ganglion was controlled in several cases by means of a scale and an ocular reading system. The size of the micro-electrodes used in these experiments varied between 5 and 50μ. The optimal size for recording the activity in single units on preganglionic stimulation was found to be about 10μ, the resistance being then about 3 megohms.

The electrical recording system (designed by Mr. A. M. Grass) consisted of a capacity-coupled, push-pull amplifier connected with a cathode-ray oscillograph. On account of the high electrode resistance, 10-megohm grid-leaks were used. The frequency characteristic of the system showed attenuation of the low frequencies, marked below 100 cycles per sec.

The stimulating shock to the nerve was derived from a thyratron set, similar to that used by Renshaw *et al.* (1940). To reduce the stimulus artefact a Wagner ground was used between the stimulating leads. The discharge of the thyratron was controlled by the sweep of the cathode ray, which in its turn was released by a hand-operated key. When repetitive stimulation was used the discharging circuit was controlled by a beat-frequency oscillator. Records were taken alternately with the micro-electrode and the wire electrode on the surface of the ganglion, in each case using the gross wire electrode on the postganglionic nerve trunk as a common lead.

Results

General observations. Two factors largely determine the pictures obtained from the superior cervical ganglion with a micro-electrode, namely, the size and position of the latter. If the micro-electrode is inside the ganglionic sheath and a large number of neurons are responding, an electrode larger than 15μ can hardly reveal the activity of a single unit, but gives the picture of a ganglionic response split up in several groups. Decreasing the strength of stimulus until background activity of remote neurons subsides may bring out some well-defined spikes. But if the aperture of the micro-electrode is smaller (5 to 10μ) the single spikes are often bigger and well distinguished. Hence, the clearest pictures are obtained with a submaximal stimulus and a small micro-electrode in a suitable position.

The effect of the position of the micro-electrode is the more pronounced the smaller the electrode. Within the ganglion a change of less than 0.1 mm. suffices to change the pattern. When the micro-electrode is on the surface of the ganglion the picture obtained is largely independent of the electrode

size and resembles closely the record obtained with gross wire leads (cf. Fig. 1A and B).

Large waves recorded with the micro-electrode are sometimes seriously disturbing. In several cases the reason for these waves has been found to be

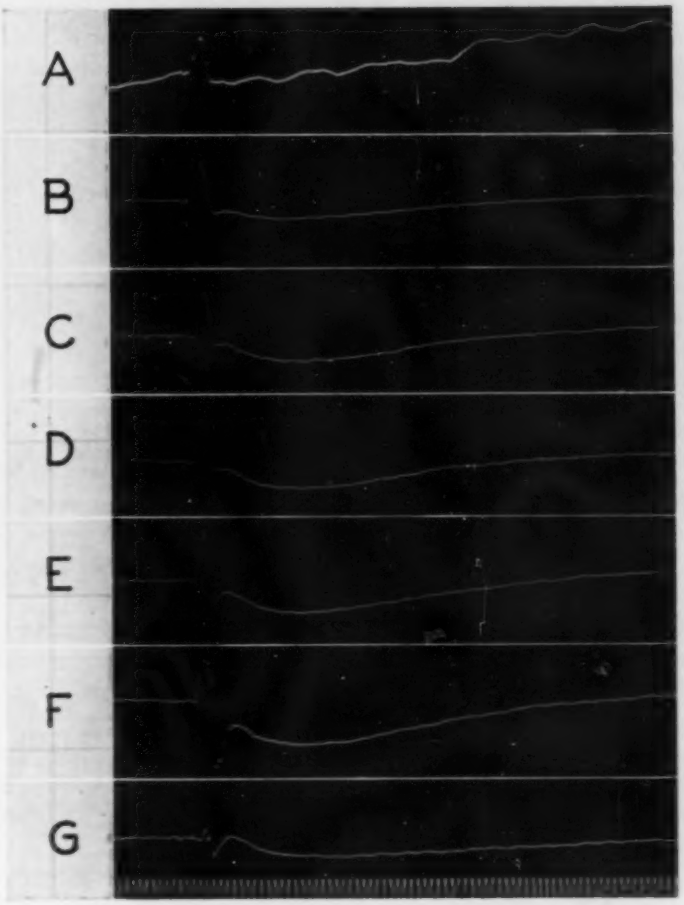

FIG. 1. Standard ganglionic response (B) with gross wire electrodes on surface of ganglion compared with records obtained with micro-electrode (aperture 30μ), with a common reference electrode on the crushed postganglionic nerve trunk. A: micro-electrode on the surface of the ganglion. C to G: micro-electrode pushed stepwise farther into the ganglion. Note similarity between A and B: corresponding increase and decrease of first positive wave and the slow positive after-potential. Maximal preganglionic stimulation. Time in 5 msec. at bottom of figure. In this and all subsequent figures, upward excursion signifies negative potential of the electrode on or in the ganglion.

passive movements of the ganglion due either to respiration or pulse. Further immobilization of the ganglion or choosing another spot for the micro-electrode has often eliminated this disturbance. When the big waves (often

of the order of millivolts) have subsided there still remains a low-voltage slow oscillation of the baseline of unknown origin (cf. Eccles, 1936).

Figure 1 shows some typical records obtained with a large micro-electrode in different positions compared with the standard ganglionic response obtained with gross wire leads (B, hereafter called "standard lead"). In Fig. 1A the micro-electrode is on the surface of the ganglion and the record is strikingly similar to that in Fig. 1B, obtained with standard lead, but as soon as the electrode penetrates the sheath the shape of the response is largely determined by the position of the electrode, as seen in Fig. 1C to G. A large positive wave following the spike potential is often a characteristic of the micro-electrode record. Its beginning and maximum are to a large extent determined by the position of the micro-electrode. It appears in close relation with the preceding spike potential. The slow positive after-potential also seems to be related to this early positive wave. This is indicated in the records by a corresponding increase or decrease in both waves. Their mutual dependence may, however, be obscured when smaller micro-electrodes are used because the frequency characteristic of these electrodes attenuates greatly slow waves such as the positive after-potential. Part of the early positive wave may be due to a ganglionic surface potential led off from the postganglionic lead. Yet the great variability of its duration and latency of the spike maxima indicates that the early positive wave differs in many respects from the main ganglion potential. Furthermore the early positive wave changes its size and latency as the micro-electrode is moved. The change, however, is less pronounced than that of the negative spikes preceding it.

Between the early positive wave and the slow positive after-potential a negative deflection is generally recorded. This may in some cases be of a considerable size and reach the baseline or even cross it before it is succeeded by the slow positive after-potential.

In general the activity revealed by a micro-electrode inside the ganglion is of a considerably greater voltage than the ganglionic response as obtained by one electrode on the surface and the second on the crushed postganglionic nerve trunk.

"*Axon-like*" *spikes.* When the aperture of the micro-electrode is made smaller the main ganglionic response becomes progressively more broken up into briefer excursions, and new groups of spikes appear until a state is reached in which the recorded action potentials show an all-or-none character. In the superior cervical ganglion such spikes are best recorded with a 7 to 10μ electrode. With a maximal preganglionic stimulus spikes can be obtained from almost any part of the ganglion and they may occur after any latency within the range of the standard ganglionic record. Only a few spikes in each record are easily recognized, however, and in most cases only one spike is of considerable height. In Fig. 2 are shown some typical records obtained with maximal preganglionic stimuli. It is obvious from Fig 2B that the diffuse background activity from remote neurons to some extent

obscures the single-spike potentials. However, by moving the micro-electrode it is sometimes possible to record an almost uncomplicated single spike, as in Fig. 2D.

In the experiments in which submaximal stimuli have been used, it was found necessary to explore different parts of the ganglion at different depths with the micro-electrode until the local activity of a single unit was recorded.

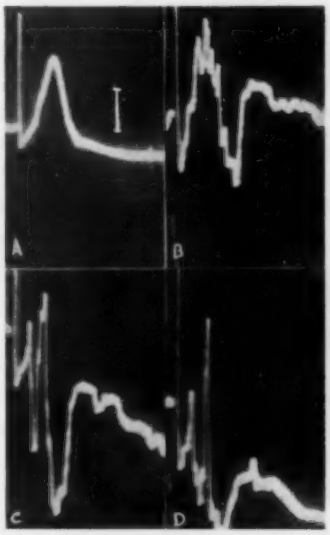

FIG. 2. Maximal preganglionic stimulation. A: ganglionic response with standard lead (gross wire). B, C and D obtained with a micro-electrode of 10μ aperture in different positions within the ganglion. Amplification the same in all records (200μV. shown by vertical line in A). Time: small squares in abscissae equal to 1.4 msec. Time of stimulus shown by artefact at the left of each record.

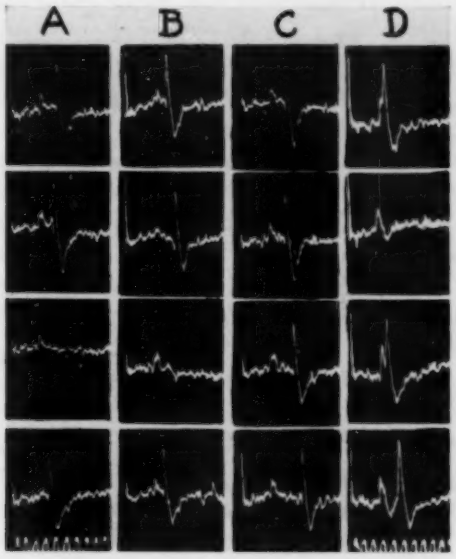

FIG. 3. "Axon-like" spikes recorded with unaltered position of the micro-electrode (aperture 7μ) but with different strengths of preganglionic stimuli, increasing from A to D, but still submaximal. The records in each vertical column were taken in one sequence without change in the strength of stimulus at an approximate frequency of 1 in 10 seconds. Note the all-or-none character of the spikes as well as the great variability in latency. Stimulus artefact appears at the left in nearly all records. Time in 2 msec.

Figure 3 shows a sample of spike potentials recorded with a 7μ micro-electrode and submaximal stimuli.

The all-or-none character of the recorded spikes is emphasized by the fact that their size or shape is independent of the strength of the stimulus and by their complete absence in some records taken in one sequence (cf. Fig. 3A, B, C, D). This sudden failure is also seen during a repetitive stimulation at maximal strength sufficient to depress greatly the ganglionic response in a few minutes. In these cases the spikes, superimposed on the

ganglionic response, suddenly drop out after a certain time of stimulation.

The duration of the spike potentials as measured at the level of the baseline varies between 1 and 2 msec. and is constant for the spike response to successive stimuli with the micro-electrode in an unaltered position. The size of these potentials may approach 500μV. and is often greater than the corresponding ganglionic potential recorded with surface leads (cf. Fig. 2A and D).

The latencies of the spike potentials, as measured from the stimulus artefact (4 to 5 cm. preganglionic conduction), have shown a wide range covering the usual duration of the ganglionic potential. Spikes with longer latencies are usually found at the cephalad end of the ganglion, but latencies up to 20 msec. have also been recorded from the caudal part. In most of the cases the latencies are found to correspond to the maximum height of the ganglionic response with standard leads. Yet significant variations in the latency of the individual spike potential have also been observed. Thus for instance the latency of the potential seen in Fig. 3, varied between 7 and 12 msec. This variation was studied especially with submaximal stimuli and was found to be largely independent of the frequency of the stimuli. Thus the variation occurred when the preganglionic nerve trunk was stimulated at rates varying from 1 per min. up to 40 per sec. That this variation was not due to the excitation of different preganglionic fibers was indicated by the fact that a variation of 7 msec. of the latency was observed when maximal stimuli were used. Yet in spite of the fact that the stimuli were maximal, this spike potential was often absent. The cause of this failure could not be determined. It occurred at low frequencies (1 per min.) as well as at high. As the stimulus frequency increased, the irregular failure of individual responses became more frequent. The relation between the resulting total frequency of response and that of stimulation is shown in Table 1. Yet even when this correlation was at a minimum, response followed stimulus with latencies showing only the above-mentioned variations. When the rate of stimuli was 40 per sec., the spike potential disappeared from the record in about 30 sec. and at a time when most of the ganglionic potential had disappeared.

With respect to the shape of the spike potentials there is usually an indication of a break at its descending phase (cf. Fig. 3). After this break the drop of the potential is less rapid and this late phase of the spike is followed by the first positive wave, which, though slower than the negative spike, is much more rapid than the positive after-potential. The magnitude of this early positive wave, as well as its duration, shows great variability with respect to spikes recorded from different positions and also to successive spikes recorded with unaltered electrode positions. Its size may be as much as half of the preceding negative spike and its average duration 2 to 6 msec. A relationship between this early positive wave and the slow ganglionic after-potential has been indicated above.

Besides the spike potentials the record shows a low-voltage spike-like

activity which is at times indistinguishable from the noise of the amplifier. The magnitude of these spikes is usually not more than about 50μV. The latency to the earliest group of these low-voltage spikes is about 5 msec.; they constitute the most persistent part of the micro-electrode record during repetitive stimulation. A careful study of the records reveals in several cases a fast regular rhythm (about 1000 cycles per sec.) immediately preceding the main spike potential and at the same time or separately a slowly rising potential.

In the absence of electrical stimuli, a slowly subsiding injury discharge has often been observed when the micro-electrode is pushed farther into the ganglion (Fig. 4). This discharge is especially clear when small micro-electrodes are used, and may take the form of a single-spike potential. These spikes are, however, often followed by very large positive "after-potentials." The injury discharge may even lose the negative spike while the positive wave still continues to appear (see Fig. 4).

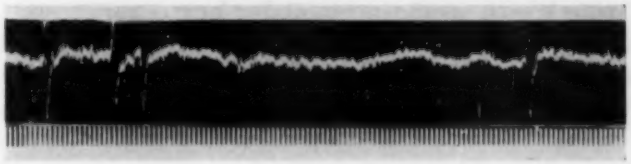

FIG. 4. Injury discharge (no electrical stimulation) obtained with a micro-electrode of 10μ aperture. Note fast "axon-like" spikes followed by large positive waves and the appearance of positive wave without a preceding negative spike. Time in 2.5 msec.

A few experiments were carried out on rabbits and essentially the same kind of records were obtained. Several attempts have also been made to reveal a single-spike activity with micro-electrodes inside the pre- or postganglionic nerve trunks. While spikes of a low voltage hardly exceeding 50μV. were recorded together with the integrated potential, none of the spikes were comparable to the large spikes obtained with micro-electrodes in the ganglion.

DISCUSSION

With a similar micro-electrode technique Renshaw *et al.* (1938, 1940) have recorded fast "axon-like" spikes from the cell-layer of the hippocampus region. These potentials were interpreted as due to the activity of the cell bodies but not necessarily confined to a single unit. A similar point of view has also been suggested with respect to the spike potentials recorded from the superior cervical ganglion (Therman and Forbes, 1939). The present study emphasizes the all-or-none character of the spikes in the ganglion. With respect to their possible point of origin all the available data strongly support the view that the "axon-like" spike potential represents the discharge of a single cell. It is evident that the spikes are postsynaptic phenomena, both because of their disappearance during prolonged repetitive

stimulation (cf. Orías, 1932; Rosenblueth and Simeone, 1938) and the great variability of the latency. That they cannot be due to the action potentials of presynaptic myelinated nerve fibers is indicated by the latency, which in some cases may exceed 20 msec., while responses conducted along those fibers should appear among the group of M_1 spikes (Bishop and Heinbecker, 1932) with a latency of less than 10 msec. Because it has not been possible to record similar spike potentials from either the preganglionic or postganglionic nerve trunks it is difficult to attribute those spikes to the activity of unmyelinated nerve fibers. Furthermore, the spike-duration is shorter than generally assumed to be the case in C fibers (Bishop, 1934; Gasser, 1937, 1938). The suggestion that these "axon-like" spikes actually are due to the electrical activity of a single cell is strongly supported by their all-or-none character and brief duration (1.5 to 2 msec.). Furthermore, they are best recorded with small micro-electrodes with an aperture of 7 to 10μ and are sharply localized. Thus the ganglion cell remains as the most probable source of these spike potentials; in fact we have been unable to find any other explanation which would account for our observations. The size of the most common type of cell in the superior cervical ganglion ranges between 15 and 30μ (de Castro, 1932). It is likely that a small micro-electrode (*e.g.*, 10μ in diameter) close to the cell surface is capable of recording a localized potential gradient with respect to a remote point on the postganglionic nerve trunk. This is emphasized in most of the records in which the spike potentials actually are bigger than the integrated ganglionic potential as obtained with surface electrodes. The large injury potentials may also be recalled in this connection as indicating that the position of the micro-electrode is close to their point of origin.

The great individual variability of the latencies of some single-spike potentials is significant. Although the frequency of the stimulus was not more than 1 in 10 seconds, in one case (submaximal stimuli) the latency varied between 7 and 12 msec., in another (maximal stimuli) between 12 and 19 msec. Effects of preceding excitation lasting even a minute or more have been demonstrated by Bronk and his associates (Bronk, 1939) in the stellate ganglion. Also the multiple innervation of ganglion cells may be recalled in this connection (cf. Eccles, 1935b), but the ultimate cause of these changes in latencies remains obscure.

The experiments with repetitive stimulation have clearly emphasized the fact that the postsynaptic neurons may discharge at rates which do not correspond to the frequency of the preganglionic stimulation (cf. Bronk, 1939). Although the discharging frequency never was higher than about 4 per sec. and actually became slower at higher stimulating frequencies (cf. Table 1), a complete block was obtained on continued stimulation (cf. Bronk and Pumphrey, 1935; Rosenblueth and Simeone, 1938).

With respect to the sequence of potential changes of active single units recorded with micro-electrodes, the method does not yet permit any conclusive comparisons with known features of after-potentials in peripheral

nerves. It can merely be pointed out that the break in the descending phase of the single-spike potential indicates the presence of a negative after-potential electrically comparable with the negative after-potential of nerve. This negative after-potential passes over into the early positive wave, which is separated by another negative deflection from the slow positive ganglionic after-potential. These two positive waves have been shown to be related in size, but are always separated by a negative wave. The potential sequence from the first positive wave through negativity and ending in the slow positive after-potential resembles the two positive after-potentials in nerve described by Gasser (1935, 1938); but it should be noted that whereas the

*Table 1**

Frequency of stimulus (Sec.)	Frequency of response	Duration of record (Sec.)
8 max.	0.4	12
18 max.	1.9	7
18 submax.	1.3	7
18 max.	1.6	9
30 max.	3.8	7
40 submax.	2.4	8
40 max.	2.4	10

* All measurements in seconds.

early positive wave of the ganglionic potential lasts about 5 msec., the first positive after-potential described by Gasser may last as much as 50 msec. There is the possibility that diphasic effects may play a part in determining the observed form and duration of the waves. We have not the data with which to analyze this possibility.

The persistence of an early group of low-voltage spike potentials during repetitive stimulation suggests that the micro-electrode to some extent is able to record the electrical activity of presynaptic fibers. Delayed small spikes may again partly be due to activity in postsynaptic fibers.

Summary

The electrical activity of the superior cervical ganglion of cats and rabbits has been studied with micro-electrodes. The recording system consisted of a capacity-coupled, push-pull amplifier and a cathode-ray oscillograph.

"Axon-like" spikes are obtained during preganglionic stimulation or as an injury discharge with micro-electrodes of 7 to 10μ apertures. The spikes are postsynaptic phenomena and show an all-or-none character and a duration of 1.5 to 2 msec. They are found dispersed over the time range corresponding to the standard ganglionic record.

The brief duration, sharp localization and all-or-none character of the spikes recorded with the smallest micro-electrodes strongly suggest that they are derived from single cells.

Study of the single-spike potential during successive stimuli and with

an unaltered position of the micro-electrode has shown variations of latency as great as 7 msec. In some cases the frequency of response is different from and largely independent of the frequency of the preganglionic stimuli.

The "axon-like" spike is followed by one negative and two positive after-potentials, the last being identical with the slow positive after-potential of the ganglionic record.

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EFFECT OF CORTICAL LESIONS ON AFFECTIVE PUPILLARY REACTIONS*†

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THE WORK of Déjerine (1906), Roussy (1907) and Head (1912, 1920) has established the importance of the thalamic level for pain sensibility. That pain may enter into awareness at the thalamic level was first stressed by Déjerine, and Roussy described the "syndrome thalamique" in which thalamic lesions cause contralateral hemianesthesia, hemiataxia, choreoathetoid movements and intense but poorly localized pain. Head utilized his clinical observations to extend to sensory activity the concept of "levels of function" which Hughlings Jackson had applied principally to the motor apparatus. Head maintained that stationary lesions involving the somatic sensory areas of the human cortex did not raise the threshold for pain perception, while such functions as light touch, two point discrimination, stereognosis and the discrimination of fine temperature differences may be markedly diminished or abolished. These studies have since been extended by Penfield (1937) who agrees that pain has little or no cortical representation. The concept of "thalamic release" was further advanced by Head to those cases in which cortical lesions caused a heightened response to pleasurable as well as to painful stimuli. Evidence that central pain of organic as well as of psychogenic origin may be caused by thalamic hyperactivity has been presented by Foerster (1927) and also by Storring (1938).

By the method of local strychninization Dusser de Barenne (1931) demonstrated a gross localization of somatic sensibility in the thalamus of the cat. In later studies (1938) on the monkey he indicated that sensory activity depends upon a reciprocal thalamocortical system. Complex pathways capable of inhibiting the thalamus by way of the cortex and striatum were delimited. These previous studies suggested the need for a simpler experiment capable of separating the function of the thalamus from that of the sensory cortex, and which could perhaps serve as a "thalamic indicator" in the intact animal. To this end the following method was devised.

METHOD

Adult cats of 2–3 kg. were used. The brain was exposed by a subtemporal approach, and the sensory area of the contralateral hind leg, as delimited by Dusser de Barenne (1916) and by Bard and Brooks (1934) was removed, either by a lateral incision into the brain substance, or by electrocoagulation. This sensory area comprises the rostral half of the longitudinal gyrus (lateral gyrus of Winkler and Potter). Part of the laterally adjacent supra-Sylvian gyrus, and that part of the sigmoid gyrus lying back of the excitable hind leg motor area was also removed. In 2 animals the motor area was included, and in 2 others more extensive cortical lesions were produced. In all animals the legs deprived of

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cortical representation showed a permanent loss of the dorsal placing reaction of Bard with preservation of the reactions on the normal side.

On each of these animals the following experiments were begun 3 weeks after the operation. The animals were placed in a box with a head holder which kept the head fixed, but allowed free observation of the eyes. After a variable period of training, lasting from 3 to 25 days, the animals would remain quiet throughout the experiment. Thus, no anesthesia was necessary. Unipolar electrodes were attached to the legs, making contact at the middle toe pad. As a stimulus an alternating current one sec. in duration upon which a constant "break" of 8 to 10 times per sec. was superimposed, passed through an inductorium with the hammer out of circuit. All sources of conditioning to the stimulus were

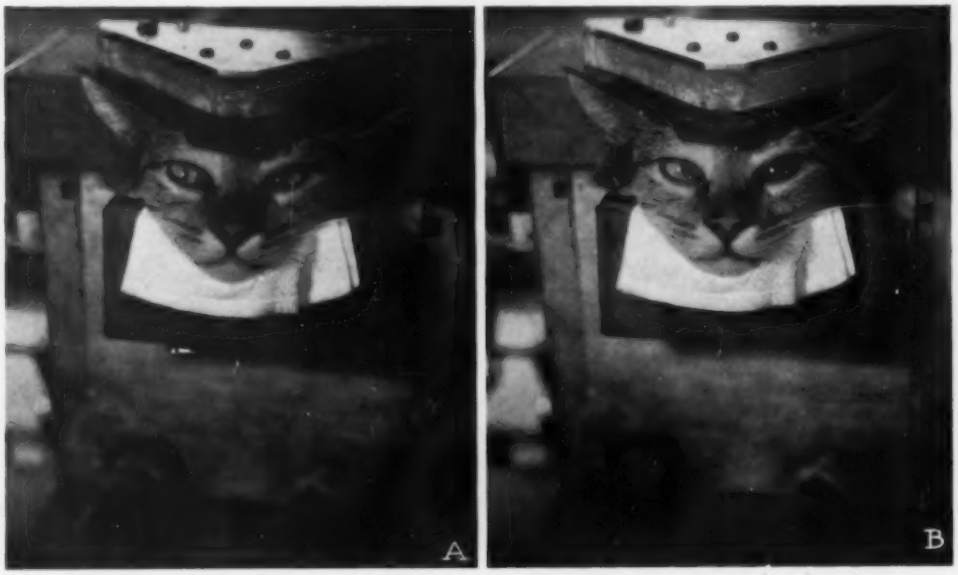


FIG. 1. Photographs of cats in experimental set-up, A. Before stimulation, and B. After stimulation.

avoided. The alternate thresholds required to elicit pain reaction from stimulation of both normal and cortically ablated legs were then recorded at one minute intervals. The pain reaction chosen as the indicator was the reflex dilation of the pupil which is mediated solely by central inhibition of the Edinger-Westphal nucleus.* As a control for the present experiment 2 cats were prepared with unilateral vago-sympathectomy. Both eyes responded with dilation at the same threshold, proving that the threshold was determined by a central inhibition, which evidently is capable of reflecting changes in the higher levels of the neural axis.

The animals with cortical lesions were placed in the box, and the head illuminated by a strong, constant light. The eyes were observed through a low-power microscope, fitted with a graduated scale, on which one division equalled 1 mm. of pupillary diameter. A dilation of one division was considered sub-threshold, and a dilation of 2 divisions as the threshold reaction (Fig. 1). This reaction occurs within the second of stimulation, and is reversible in from 1 to 2 seconds. The pupillary reaction is the constant and unfailing precursor of more violent pain reactions, such as moving or crying. A shortening of the coil distance, 0.5 cm. from the point which gave the threshold pupillary reaction, gave

* That this reaction is exclusively an inhibition has been stated by Bechterew (1883), Braunstein (1893) and Bain, Irving and McSwiney (1934). Ury and Gellhorn (1939) have extended these observations.

these stronger, more generalized reactions. Both eyes react simultaneously and to the same degree, irrespective of the leg stimulated. Under these experimental conditions the dilation of the pupil in response to an afferent stimulus is a constant, sensitive indicator of a central process associated with pain. It is caused by a central inhibition, and is uncomplicated by any variable factors in the periphery.

The preceding method was devised to differentiate the role of the cortical somatic sensory areas from that of subcortical sensory levels, especially the thalamic. However, since Karplus and Kreidl (1910) obtained pupillary dilation from stimulation of the frontal cortex of the cat and from area 8 of the monkey, an additional method was used to study this cortically initiated reaction. Cats were prepared similar to those used by Ury and Gellhorn (1939) in which one pupil was deprived of its oculomotor innervation and constricted with eserine, while the other was sympathectomized. Five days post-operatively the the calvarium was removed under local novocaine infiltration and the cortex stimulated by bipolar electrodes, 1 mm. apart. The cortical areas giving threshold pupillary reactions by either oculomotor inhibition or sympathetic discharge were then plotted.

Results

Results of individual experiments on animals with cortical lesions are best expressed by the submitted graphs (Fig. 5 and 6). The following table summarizes the results.

Table 1

Animal No.	1.	2.	3.	Total
4	13	1	2	16
5	10	3	1	14
6	10	0	1	11
7	9	1	1	11
10	0	8	0	8
11	7	0	1	8
8	13	2	3	18
14	10	0	0	10
12	3	11	0	14
17	4	8	1	13
	79	34	10	123

Column 1. Number of experiments showing no differences in reaction on either side.
Column 2. Number of experiments showing ablated side more sensitive.
Column 3. Number of experiments showing normal side more sensitive.
Animals with sensory ablation: 4, 5, 6, 7, 10, 11.
Animals with sensorimotor ablation: 8, 14.
Animals with massive lesion: 12, 17.

Sixty-one experiments were performed on 6 animals which had ablation of the sensory cortex. Of these, 13 experiments showed the ablated side to be more sensitive by 0.5 cm. on the threshold determination. Of these latter, 8 experiments occurred in Cat 10 which showed a small but constant increased sensitivity on the ablated side. At autopsy nothing unusual was found to account for this fact. Six experiments showed the normal side to be slightly more sensitive; 49 experiments showed no difference.

Twenty-eight experiments were performed on 2 animals with sensorimotor lesions. Of these, 4 showed the normal side more sensitive, and in 2 the ablated side responded at the lower threshold, while 22 showed no difference.

Twenty-six experiments were carried out on the 2 animals which survived extensive cortical lesions. Of these, 19 showed a marked lowering of the threshold on the affected side, and one isolated experiment showed the normal side more responsive.

All the lesions were verified by stimulation of the post-cruciate motor area either on the normal or affected side. The brain of one animal of each group was sectioned and every tenth section stained alternately with Nissl and Weil's myelin sheath stain. The sections were cut in the plane indicated by the monograph of Winkler and Potter (1914), whose nomenclature and topographical divisions are utilized in this paper.

HISTOLOGICAL STUDIES

CAT 4 was selected as typical of the animals with sensory lesions. Nissl section 180 at the level of Pl. 2 of Winkler and Potter shows the motor area bilaterally intact. Cortical destruction included the longitudinal gyrus with extension to the adjoining posterior portion of the sigmoid gyrus. Medially, the lesion reaches the sulcus splenius. This confirms the destruction of the sensory area of the hind leg as shown by permanent loss of the placing reaction. The subcortical structures are intact, and there is a slight loss of cells in the nucleus ventralis.

CAT 8, one of the animals with lesion of the sensorimotor cortex is shown in Fig. 2. The focal point of the electro-coagulation is in the rostral half of the longitudinal gyrus with the destruction spreading to the cruciate sulcus, which is obliterated on the left. Nissl section 250, between Pl. 2 and 3 of Winkler and Potter shows destruction of the cruciate sulcus on the left with the region beneath occupied by a dilation of the lateral ventricle. There is gross destruction of the cell layers in the cortical areas 5 and 7 in which lie the sensory areas of the hind leg, and a destruction of the nerve fibers in the centrum ovale leading to this area. This confirms the physiological evidence delimiting the lesion, which showed a permanent loss of the dorsal placing reaction on both right legs and an extensor rigidity lasting 3 weeks on the right hind leg. All subcortical structrues are intact.

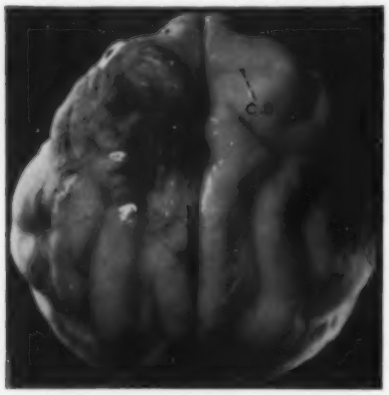


FIG. 2. Photograph of brain of Cat 8, with sensorimotor lesion.
C. S., Cruciate Sulcus.

CATS 12 and 17 are animals with massive cortical lesions. On Cat 12 an extensive unilateral cortical electrocoagulation posterior to the motor area was carried out by one of us (E.O.) on August 11, 1937. Upon recovery the animal showed a permanent loss of the dorsal placing reactions of Bard on both left legs, while the right responded normally. This animal showed marked extremes of behavior, either being unusually quiet and docile or extremely excitable. At no time did it show pupillary inequality, and all through the experiments both eyes reacted at the same threshold and to the same degree. This bilateral reaction was evoked at a lower threshold when the hind leg contralateral to the lesion was stimulated. Usually the eye homolateral to the leg stimulated was used as the indicator, but in several experiments a single eye was used throughout without altering the result. The destruction of pupillo-constrictor neurons in the right occipital cortex does not account for the differential obtained in afferent stimulation, but made the entire pupillo-constrictor apparatus more sensitive to inhibition.

The "release" phenomena observed in this animal showed great variability, and in 3 experiments this was not obtained. For a time this "release" seemed to decrease but a later experiment, on May 20, 1938, showed this effect to have regained its initial magnitude.

In these experiments an important factor which determines the threshold is the resistance of the skin to the passage of the stimulating current. Sweating decreases this resistance. To evaluate this peripheral factor, readings were taken of the skin resistance of the toe pads by C. W. Darrow. This showed the resistance of the normally represented leg to be 7,000 ω, while the figure for the cortically ablated leg was 11,000 ω. Thus, any difference in peripheral permeability would increase, and not lower the threshold of the leg with cortical lesion. This result agrees with the work of Bucy (1935), who found that cortical lesions first increase, but later decrease the sweating on somatic areas which they influence.

CAT 12. *Summary of microscopic study.* The animal was anesthetized and the brain exposed. In attempting to remove the adherent leptomeninges, softened brain tissue exuded and an artificial opening was made into the lateral ventricle. After injection with 10 per cent formalin, the brain was removed and routinely sectioned, every tenth section being stained alternately with Nissl's method and Weil's myelin sheath stain.

Extent of the lesion. Grossly, the destruction of the cortical tissue includes the middle and posterior part of the parietal lobe, the occipital and temporal lobes. Microscopic study, however, shows that the lesion begins just posterior to the cruciate sulcus. Section 220, which lies midway between Pl. 2 and 3 of Winkler and Potter, here borders the lesion rostrally. Nissl section 210 shows area preparietalis 5, which contains agranular cortex, to be normal; while posteriorly area preparietalis 7, which is the rostral border of the sensory area, is destroyed. Medially the lesion ends at the sulcus splenius, while laterally the gyrus lateralis (longitudinal gyrus of Bard and Brooks) and the gyrus supra-Sylvius are destroyed. The caudate nucleus is distorted, being pulled out in a vertical and lateral direction, and at its most dorsal point just touches the lesion, which invades the corona radiata. Microscopic study of the caudate nucleus on the affected side shows marked vacuolization of the ganglion cells, gliosis and neuronophagia due to direct influence of the lesion. The left (normal) caudate shows only slight gliosis. On the normal side the section passes through cortical areas 1, 5 and 7. These areas represent the sensory area of the normal hind leg, and show slight gliosis but no marked abnormality. This confirms the physiological integrity of this area as shown by the placing reaction.

Figure 3 is a reproduction of section 460 stained with Weil's myelin sheath stain. This and contiguous Nissl sections delimit the following pathology. Medially the cortical lesion includes the gyrus supra-splenius and sulcus splenius. Laterally the lesion extends to the gyrus Sylvius posterior, including the gyrus lateralis and gyrus-Sylvius. There is destruction of the corona radiata and some invasion of the internal capsule.

The fornix system is bilaterally intact with no invasion of any ventral-lying structures, and the peri-ventricular system comprising the nuclei ependymalis, nucleus reuniens and the medial nuclei are bilaterally normal. The right thalamus is slightly smaller than the left, with the following changes in the right thalamus. Nucleus anterior a is one-half the size of the control nucleus, its capsule of myelinated fibers is decreased; and there is a marked loss of ganglion cells and gliosis. There is a loss of cells in the ventral portion of nucleus lateralis a, and diffusely in nucleus ventralis b. The lateral geniculate body on the right shows marked shrinkage, a loss of surrounding mylein sheaths, and almost complete loss of ganglion cells. At the caudal portion of the occipital lobe a section corresponding to Pl. 19 of Winkler and Potter shows the cortical lesion to extend from the sulcus supra-splenius medialis to the sulcus supra-Sylvius posterior. The entire cortex of the left (normal) side shows only a slight gliosis, confirming its physiological integrity shown by the placing reaction.

CAT 17 is the second animal which survived massive cortical ablation. Here the occipital cortex was spared. The operation was done October 18, 1938, and in 5 experiments performed during the succeeding month, 4 showed no difference in threshold between the two sides, and one experiment showed the normal side more responsive. In the 8 succeeding experiments done since November 1938, all showed the ablated side to be more sensitive by a difference of 0.5 to 1.0 cm. on the threshold determination. Rough subjective tests show that in this region of the inductorium a decrease of 1.0 cm. results in a doubling of the stimulus delivered.

A summary of the foregoing histological study is as follows: (i) *Sensory lesions:* Destruction of the cortical area representing the hind leg. No subcortical involvement. Cortex of the control leg uninvolved. (ii) *Sensori-motor lesion:* Destruction of the excitable motor area and sensory area of the hind leg. Cortex of the control leg uninvolved. (iii) *Massive*

cortical lesion: Destruction of the cortex from the sigmoid gyrus to the occipital cortex on the right. Slight gliosis of the normal cortex. Subcortical involvement on the right as follows: (a) Marked pathologic changes in the caudate nucleus. (b) Marked loss of cells in the anterior nucleus of the thalamus. (c) Destruction of the geniculo-striate system.

To what extent each of these factors is responsible for the experimental result cannot be decided from the data given by one animal.

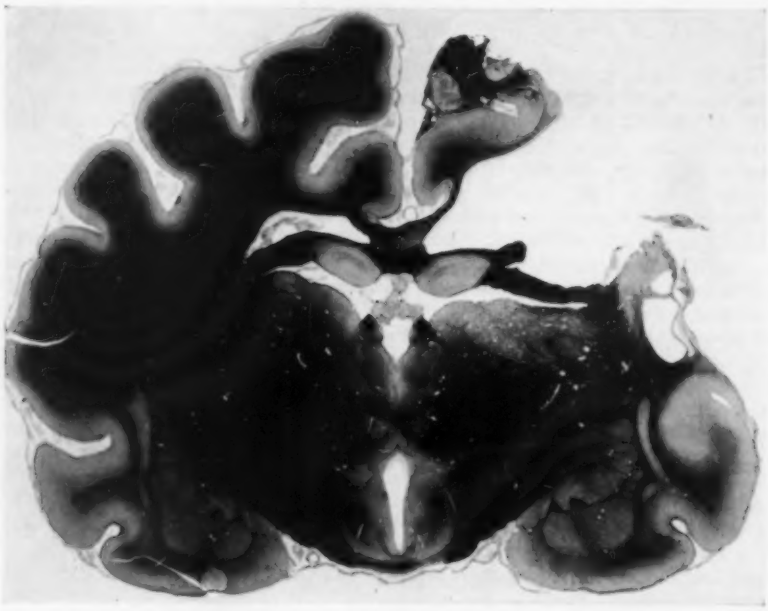


FIG. 3. Photograph of Cat 12, Section 460, level between Plates 12 and 13, Winkler and Potter.

Five cats were prepared as previously described to determine the effects of cortical stimulation. The results of these experiments will be described more fully later, but their essentials may be reported as follows: (i) Three cortical fields were found which gave the inhibitory pupillary reaction on the sympathectomized eye. These fields correspond in a remarkable way to the regions from which Tower (1936) obtained inhibition of extrapyramidal movement in the cat. Her Fig. 2 also represents our fields a and b. (a) A frontal field lying anterior to the cruciate sulcus in the gyrus proreus. This is the region from which Karplus and Kreidl (1910) obtained their pupillary reaction. This field gave the inhibitory reaction at 9.0 cm. (Harvard inductorium) and bilateral nictitating membrane retraction at 6.0 cm., without any observable sympathetic pupillary response. (b) A field lying in the anterior and posterior sylvian gyrus. This field gave only the inhibitory pupillary response at 7.5 cm. No nictitating membrane discharge was obtained with increasing stimulus. (c) An occipital field, weaker and less extensive than the preceding, which gave only inhibitory responses at 7.0 cm. (ii) No pupillary or nictitating response was obtained from the somato-sensory area of the hind leg, as previously outlined.

Discussion

The preceding experiments indicate the following: (i) The threshold of pupillary response to pain stimuli is not raised by ablation of the sensory or sensorimotor cortex in the cat. (ii) In 2 animals with massive cortical lesions the threshold to pain was lowered. (iii) The inhibitory pupillary reaction may be obtained from cortical areas not related to the somatosensory system.

At this point the question of a bilateral sensory cortical representation must be discussed briefly. Marshall, Woolsey and Bard (1937) have shown by action currents that the tactile sensibility of the entire body, excluding the face, is represented only in the contralateral cortex. In general, sensory points lie posterior and lateral to the motor points. Bilateral effects are due to diffuse activation of the thalamus either by extreme artificial stimuli or such powerful pharmacologic agents as strychnine. Dusser de Barenne (1935) attributes the bilateral effects he obtained by strychninization of the cortex as due to activation of thalamic nuclei. In the monkey, the limit of the sensory representation on the medial surface is the first sulcus buried in the medial fissure. This is the sulcus splenius in the cat. In the cat, less of the median surface is involved in the sensory radiation, which only represents the area of the perineum and tail, while the flexor surface of the hind leg lies above and lateral to this perineal area.

The experiments here reported show that the presence of the sensory cortex on the control side does not add any positive component to the indicator reaction in response to nociceptive stimuli. Therefore this threshold must be subcortically determined. Before defining these determining structures by means of the indicator reaction, a general scheme for interpreting pupillary reactions is presented.

Reactions occurring at the pupil reflect a summation of central events made evident through a peripheral mechanism. These central and peripheral mechanisms may be considered separately if the reacting structures are divided into the following 3 regional groups: (A) Mechanism of the peripheral innervation, (B) Nuclear mechanisms, (C) Supranuclear mechanisms—central pathways.

A. Peripheral innervation. The course of the sympathetic pre-ganglionic fibers to the pupil has been reexamined by Bishop and Heinbecker (1932). Sectioning of this sympathetic pathway anywhere in its peripheral course, and also at any point in its descending bulbar and spinal pathways from the hypothalamus results in a Horner's syndrome whose restitution shows a variable course depending upon the site of the lesion.

The autonomic part of the third nerve is the paired ventromedial nucleus of Edinger-Westphal. Its small-celled anterolateral portion gives off fibers which innervate the sphincter of the pupil. Recent studies by Crouch (1936) show that each iris is innervated by both the homolateral and contralateral portions of the nucleus. Each iris is, therefore, under the control of both crossed and uncrossed fibers. Conversely, each side of the

nucleus influences both pupils. This clarifies the mechanism by which both pupils react as a unit to constrictor impulses in the consensual light reflex and to central inhibition.

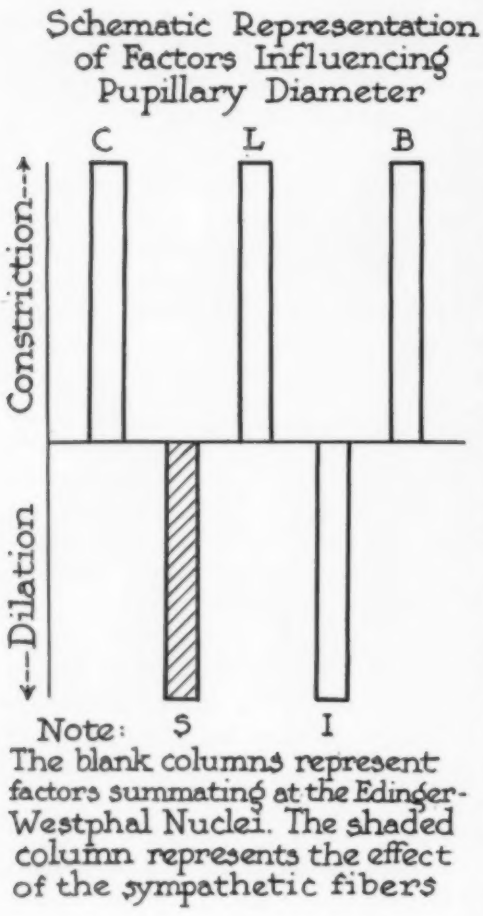


FIG. 4.

None of the variability of the pupil to light or afferent stimuli is lost when the sympathetic component is interrupted, but the magnitude of the reaction is diminished. That normally this difference is due to the tonic action of the sympathetic and not to its reflex excitation has been shown by Ury and Gellhorn (1939). This concept is valid also for the variable dilation in such a preparation upon decreasing the impingent light. Von Brücke (1931) and later Bender (1938) found no reaction to light upon section of the oculomotor nerve. Gullberg, Olmsted and Wagman's (1938) assumption that in dark adaptation the sympathetic tonus increases is further disputed by the clinical fact that in complete internal ophthalmoplegia the pupil is fixed. The variability of the pupil is therefore due to variation in oculomotor tonus, which is in itself a summation of various nuclear events.

B. Nuclear mechanisms. In relation to afferent stimuli all the factors which are summated in pupillary reactions may be represented in the following diagram (Fig. 4). *Column S* represents the sympathetic dilator tonus which may be considered invariant. Its effect is peripheral, while the 4 remaining elements enter into events occurring at the Edinger-Westphal nucleus. Their significance is as follows:

Column I represents central inhibition which acts in the dilator direction and is the measure of sensory, affective activity. *Column C* represents the cortical component of pupillary constriction, obtainable in cats upon stimulation of the visual cortex. *Column L* represents the constrictor tonus due to the light reflex, mediated by the pretectal area.

Column B represents a constrictor tonus which differs from *L* in that it is independent of the light reflex. This independent rhythmic discharge represents the "basal tonus" of the Edinger-Westphal nucleus and is seen

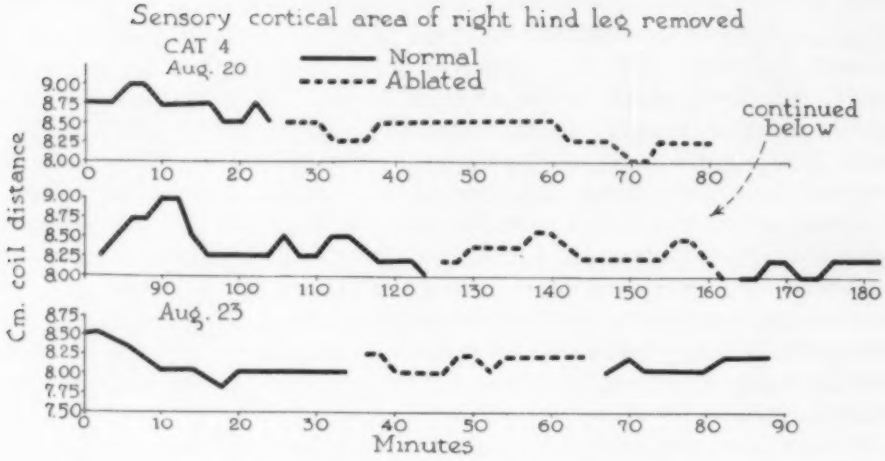
when complex superimposed pathways projecting excitation and inhibition upon this nucleus are eliminated. These pathways are evidently suppressed in sleep, coma, or deep narcosis, which are characterized by a pupillary constriction maintained in the absence of light. The "paralytic dilation" signifies the cessation of this spontaneous neural discharge and usually the death of the animal. Similar automatic, independent rhythms have been observed in other neurons and neural aggregates. Adrian (1932) led off rhythmic action potentials from the isolated brain stem of the goldfish in regions of the vagal nuclei. Libet and Gerard (1939) demonstrated spontaneous action potentials from isolated olfactory lobes of the frog, even when synaptic junctions were abolished by nicotine. That larger functional aggregates may act similarly is suggested by the Berger rhythm obtainable from the occipital cortex in absence of visual activity, and also from other cortical areas.

C. Inhibitory supranuclear pathways. Central inhibitory processes are usually projections from higher to lower levels, and therefore pathways inhibiting the Edinger-Westphal nucleus should traverse structures lying above the level of the third nerve. Since direct stereotactic stimulation of the hypothalamus causes this reaction (Ranson (1938) and collaborators) this structure may be the immediate effector organ. In preceding experiments with cortical lesions a point to point correspondence with afferent stimuli has been demonstrated. Since this reaction is extinguished by appropriate narcosis (Ury and Gellhorn, 1939a), and is further a constant expression of affective states, these afferents must reach a sensory level which contributes to awareness. The results of Bremer and collaborators (1936), especially E. Class, show that direct stimulation of the thalamus, corticothalamic tracts and other diencephalic structures yield this reaction.

The experiments reported on Cats 12 and 17 indicate overactivity of a sensory level to nociceptive stimuli. That this property is essentially thalamic has been stressed by Walker (1938), Head (1920) and Foerster (1927). Should this reaction prove to be an expression of a thalamo-hypothalamic mechanism, various anatomical pathways are at its disposal. LeGros Clark (1932) and Walker (1938) indicate periventricular fibers. Greving (1928) and Huber and Crosby (1929) stress connections by way of the striatum and subthalamus. It is these which Penfield (1929) considers responsible for the autonomic symptomatology in his case of a tumor in the anterior thalamus.

Although the activity of the little known tectal sensory level cannot be excluded as contributing to this reaction, the evidence favors the interpretation that diencephalic mechanisms are principally involved. A modification of the experimental method described here, which would determine synchronous points between the indicator reaction and the electrical activity of a given neural unit, might yield a new method for determining diencephalic relations.

The results obtained here on the somatic sensory system of the cat are



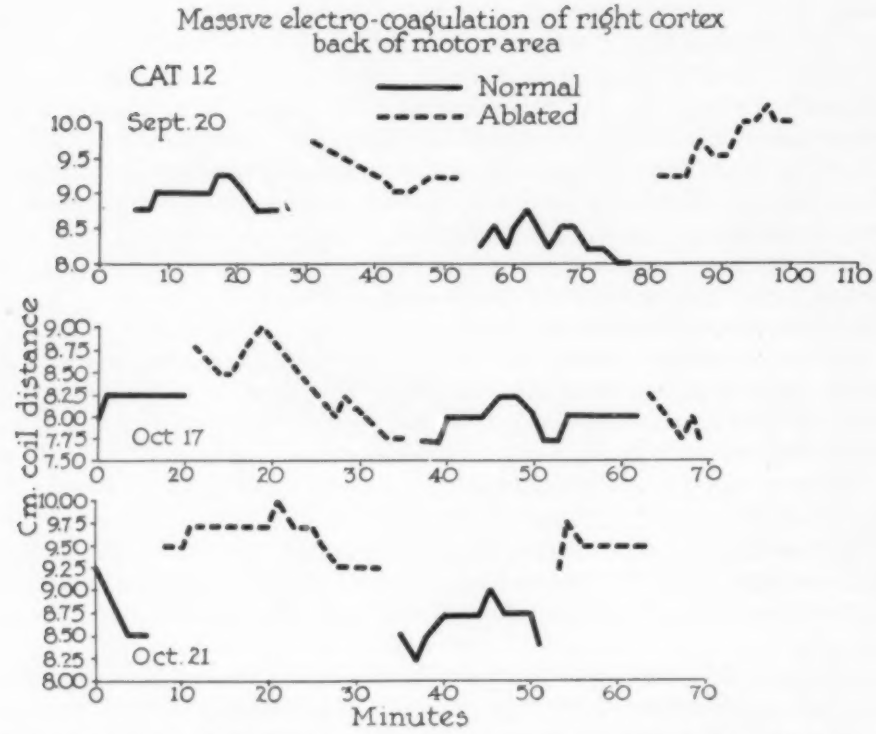


FIG. 5 and 6. The graphs show the coil distance necessary to obtain the threshold reaction. The ordinate is coil distance in cm., the abscissa is time in minutes.

in agreement with other forms of sensory intensity discrimination, especially those relating to the visual system. Lashley (1937) has shown by extended studies on the rat that destruction of the striate area permanently abolishes detail vision, leaving unimpaired the ability to discriminate light intensity,

which is determined by subcortical visual structures. Intensity discrimination is here a subcortical function, while spatial localization and sequential relationships are contributed by the cortex. In man brightness discrimination has undergone corticalization, but it is significant that pain discrimination in man as well as in animals is still effected at the highest subcortical level.

That the cortex may initiate affective pupillary reactions was shown by Karplus and Kreidl (1910). However, their viewpoint that this reaction is predominantly sympathetic will have to be revised in favor of central inhibition, as was their concept of the mechanism of reflex dilation (Ury and Gellhorn, 1939b). Our experiments also show that this reaction may be obtained from other cortical areas. This discrepancy may be due to absence of general narcosis in our experiments. The identity of these fields with those determined by S. Tower (1936) which give inhibition of extrapyramidal movement is suggestive of a common striatal factor, while the presence of a temporal field points to the affective potentialities of this area now being revealed by Kluver and Bucy (1939)

Conclusion

The threshold to pain reaction was studied on suitably trained, unanesthetized cats after varying amounts of cortex had been removed. The indicator used was the reflex dilation of the pupil caused by inhibition of the Edinger-Westphal nucleus. Cortical areas giving this reaction were also determined. The results are as follows:

1. Ablation of the sensory or sensorimotor cortex does not raise the threshold to pain reaction.
2. Massive cortical lesions lower the threshold to pain reaction.
3. Cortical areas capable of inhibiting extrapyramidal movements also cause inhibition of the Edinger-Westphal nucleus.
4. The possible pathways of the indicator reaction are discussed.
5. A general scheme for pupillary activity is presented.

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POSTURAL REFLEXES AND GRASP PHENOMENA IN INFANTS

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INTRODUCTION

TONIC NECK REFLEXES and the various types of grasp phenomena (forced grasping, grasp reflexes of the hand and foot, volitional grasping movements) have been the subject of numerous experimental and clinical investigations. Tonic neck reflexes were studied and described in infants and children by Schaltenbrand (1925), Peiper and Isbert (1927), Gesell (1934), Byers (1938), and others. Grasp phenomena in infants have been described by Watson (1919), Givler (1921), Troemner (1928), Bryan (1930), Peiper (1931), Chaney and McGraw (1932), and Brain and Curran (1932). However, relatively few observations have been made regarding the possibility of any specific relationships between the tonic neck reflexes and grasping movements in normal and pathological human material.

MATERIAL AND METHODS

In order to study the relationships, if any, between tonic neck reflexes and grasp phenomena in normal humans, a series of observations were made in 70 healthy, newborn, premature and 30 healthy, newborn, full-term infants at the Kings County Hospital, Brooklyn, N. Y. In addition, one case diagnosed clinically as amaurotic familial idiocy was studied. All infants whose birthweight was 5 lbs. or less, were considered to be premature. The smallest infant examined weighed 2 lbs. 13 oz. but the usual weight in the premature group varied between 4 and 5 lbs. Most of the premature infants were examined on at least 2 different occasions and observed over periods varying from 2 weeks to 4 months. The full-term infants were examined only on one or two different occasions at some time during the first ten days of life.

At each examination, asymmetric tonic neck reflexes were studied and observations were made upon the concurrence of grasp phenomena. An asymmetric tonic neck reflex was considered positive when rotation of the head around its longitudinal axis with the infant initially in the normal symmetrical supine position produced relative extension of one or both limbs on the "chin side" of the body and corresponding flexion of one or both limbs on the opposite side. Rotation of the head was produced by the examiner's hands, which were placed as symmetrically as possible along both sides of the head. For purposes of photography a nursing bottle was presented to the infant's mouth after rotation of the head, and in this way a constant posture of the head was maintained without the struggling which at times accompanied the manual rotation. It is well recognized that in the young infant the act of sucking may be accompanied by strong flexion of the upper limbs. In our material the upper limbs often remained in or assumed an attitude of flexion with the hands partly or firmly clenched irrespective of whether manual rotation alone or manual rotation with subsequent administration of the nursing bottle was used. In general it was observed that the tonic neck responses were more definite, and more frequently obtained in the lower limbs than in the upper limbs.

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Observations

Positive asymmetric tonic neck responses were obtained quite consistently in 64 of the 70 premature infants and in 16 of the 30 full-term infants during the course of an examination. In the remainder of the cases, the responses were variable and exhibited no constant postural pattern of the limbs upon rotation of the head through 180° of arc. In 9 of the 64 premature, and in 3 of the 15 full-term infants showing positive neck responses an initial flexion movement of the toes was fairly consistently observed in the flexed limbs while an initial extension movement of the toes was usually noted in the extended leg. In these cases, the flexion or extension attitude of the toes sometimes remained fixed in position so long as the relative flexion or extension attitude of the limbs persisted, thus appearing in the nature of a tonic response. Figures 1 and 2 illustrate flexion of toes in the flexed limb and relative extension of the toes in the extended limb. It should be noted that asymmetry in posture is definitely present in the legs as noted above, whereas the upper extremities remain fairly symmetrical in flexion. The maintenance of the position of strong flexion in the upper limbs was possibly enhanced by the presence of a sucking response. However, in this case the flexion was present before sucking was initiated. It should be noted, in addition, that the infant in Fig. 2 exhibited flexion of the toes as the right leg spontaneously flexed on rotation of the head, and the photograph was snapped as the infant rotated the leg medially. This eliminates the possibility of flexion of the toes as being associated with pressure on the sole of the foot. In Fig. 1, the relative flexion of the toes in the left foot is seen to exist with the leg in the lateral flexed position in which position pressure on the sole would not be a factor. In the remaining 55 premature and 11 full-term infants in the group showing the positive neck reflexes, a flexion-extension pattern of response of the toes was not consistently obtained. Nevertheless such responses occurred often enough to justify an interpretation that they were the dominant form of response. Other responses of the toes were also seen including at times flexion of the toes in the extended leg and extension of the toes in the flexed leg. Sometimes no changes in the positions of the toes occurred at all, even when the tonic neck reflex pattern of the limbs was very definitely positive. In some of these cases alternating flexion and extension movements of the toes in both the extended and flexed legs were often seen during the examination.

In order to study possible relationships between changes of the position of the body in space and concomitant grasp phenomena, all of the infants in the group were subjected to changes in position. The technique was to place the infant with one or the other side down either by placing the infant on its side on the bed, or by manually suspending it in the air, at the same time holding the head so that its normal symmetrical position relative to the body was maintained during these procedures. By this means, labyrinthine reflexes were prevented from changing the position of the head in relation to the rest of the body, thereby preventing any tonic neck reflexes

FIG. 1. (left) This figure illustrates the response commonly found in the group of premature infants on rotation of the head. It will be noted that with rotation of the chin to the right relative flexion of the left lower extremity and extension of the right lower extremity occurred. Associated with this, relative flexion of the toes in the left lower extremity and extension of the toes in the right lower extremity occurred. In this case asymmetry in the limb posture was not observed in the upper limbs, after rotation of the head and before the nipple was placed in the infant's mouth. The maintenance of the position of strong flexion in the upper limbs, however, was possibly enhanced by the presence of a sucking response.

FIG. 2 (right). In this case, upon rotation of the chin toward the left relative flexion of the right lower extremity and extension of the left lower extremity occurred. Simultaneously, flexion of the right toes and extension of the left toes occurred. Again, a relatively symmetrical flexed posture in the upper limbs was observed after rotation of the head, and before the nipple was placed in the infant's mouth. The maintenance of the position of strong flexion in the upper limbs, however, was possibly enhanced by the presence of a sucking response.

from coming into play. Thus, any digital flexion or flexion of the limbs which might occur as a result of changes of the entire body in relation to space could not be due to the influence of the tonic neck reflex mechanism. In the

whole group, however, no consistent pattern of response as regards flexion or extension movements in either the limbs, the toes or the fingers was obtained by this test. No definite relationships, therefore, were demonstrated in the newborn infant between the position of the body as a whole in space, and reflex postures in the limbs or toes.

In addition to the entire group of normal infants studied a case of decerebrate rigidity in a 19 month old Hebrew female child, diagnosed clinically as amaurotic familial idiocy was observed over a period of several weeks. This patient exhibited marked rigid extension of the limbs and spine with a "scissors attitude" of the legs and a position of the fingers and toes

FIG. 3. This infant is clinically diagnosed as suffering from amaurotic familial idiocy. The usual spontaneous posture of the infant was that of decerebrate rigidity with hyperextension of all the limbs and opisthotonus. The constant response consisting of flexion of the toes opposite the "chin side" and the neutral position of the toes on the "chin side" is well demonstrated.

more or less midway between flexion and extension. This posture remained fairly constant with changes of the position of the entire body in relation to space. However, upon rotation of the head with the chin to the right, with the patient remaining in the supine position, a slow flexion of the toes on the left was observed, with practically no change in the position of the toes of the right foot (Fig. 3). When the head was returned to the mid-line position again the flexed toes on the left slowly returned to their original position, but as the rotation of the head was continued through a 90° angle to the left, gradual tonic flexion of the toes on the right occurred. They remained in flexion until the head was again rotated back to its original position. No change in the posture or the gross relative rigidity of the limbs, however, was obtained as the head was rotated from one side to the other. The fingers of the hand showed relatively little change in their positions or their tone during rotation of the head.

Discussion

The above findings suggest the possibility of an interrelationship between the asymmetric tonic neck reflexes and the grasp phenomena of the toes. That this interrelationship is not primarily dependent upon mere flexion of the limbs alone is suggested by our observations. It appears, however, that there is more likelihood of flexion of the toes occurring in a limb which assumes the flexed position in response to rotation of the chin to the opposite side than in a limb which assumes or maintains an extended position under similar conditions.

The exact relationship existing between the tonic neck responses, the postural mechanism as a whole and the grasp phenomena, remains obscure. Fulton and Dow (1938) described postural neck reflexes in the labyrinthectomized monkey and their effects upon the grasp reflex, following total bilateral removal of areas 4 and 6 in the brain. In these operated monkeys they obtained release of the tonic neck reflexes and the grasp reflex, and found that any postural reaction originating from the neck or body that produces an increase of flexor posture in an extremity also causes intensification of the grasp reflex; any postural reaction causing an increase in extensor posture causes diminution in the grasp reflex. It was concluded, therefore, that grasping in primates is not an isolated reaction, but an integral part of the postural reflex mechanism. In an earlier publication, Kennard, Viets and Fulton (1934) had reported that in the human subject the strength of the grasp phenomena varies with the patient's position in space, exactly as described later for the monkey by Fulton (1934) and Bieber and Fulton (1938). The conclusion of Fulton and his coworkers that grasp is part of the righting reflex mechanism peculiar to primates was disputed by Walshe and Hunt (1936) who pointed out that it would be more accurate to say that grasping and the righting reflexes interact. They state that such interaction between reflexes of different physiological category is known to occur and in this connection mention as a case in point the influence of the tonic neck reflexes upon the Babinski response as recorded by Walshe (1923). In the study of their own cases of humans, however, Walshe and Hunt reported that they found no influence of body posture in relation to space or of head posture in relation to the trunk upon either grasping movements or upon reflex tonic grasping.

In most of the experimental material and in a great deal of the human material of other investigators, the experiments have in general dealt with either normal or pathological animal or pathological human cases. In our own material, consisting of normal human premature and full-term newborn infants and one pathological infant, we are led to believe that there is a definite effect of head posture in relation to the trunk upon grasping movements. In this latter respect our findings seem to agree somewhat with those of Fulton.

Our observations, in normal infants and in one pathological infant, concerning the relationships, if any, between grasp phenomena in the fingers

and toes and changes in the position of the body as a whole in space, however, do not seem to agree with those observed by Fulton and his coworkers for pathological animal preparations and pathological human material.

Conclusions

On the basis of our findings in human infant material, we feel justified in concluding that a relationship of some degree of concurrence exists between the tonic neck reflex mechanism and the grasp phenomenon, but that the latter is not necessarily an integral part of the tonic neck reflex mechanism. In addition, our material discloses no relationship of concurrence between changes of the position of the body as a whole in space and grasp phenomena.

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ACTION OF ETHER AND NEMBUTAL ON THE NERVOUS SYSTEM

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INTRODUCTION

EXPERIENCE has shown that potential records of activity in the central nervous system are too complex to permit easy analysis. This is a consequence of anatomical complexity which makes difficult the recording, except to a limited degree, of activity potentials of specific units. To determine the mode of action of an anesthetic on the nervous system it was decided to follow the plan, used in the study of strychnine action (Heinbecker and Bartley, 1939), of obtaining data on the effect of the agent on structures like the axon, the synapse, and the ganglion cells of the median nerve cord of *Limulus* heart which lend themselves readily to experimental attack. The results are utilized in an explanation of the more complex action of these agents on the central nervous system. While the extent to which it is permissible to interpret activities of the central nervous system in terms of the properties of peripheral axon, synapse and ganglion cell is still debatable, recent evidence indicates that comparable structures in the central and peripheral divisions of the nervous system act similarly qualitatively, but they may have different time relations.

The effects of ether and nembutal on the frog axon, on the turtle peripheral synapse, on the median nerve cord of the heart of *Limulus polyphemus*, on the spinal cord of turtle and on central nervous system of cat are here reported. It is assumed that activity in corresponding units of the nervous system of various animals will be qualitatively similar. Owing to the extent of the subject matter covered no attempt will be made to analyze the literature. Others, among them Derbyshire, Rempel, Forbes and Lambert (1936), have followed the action of anesthetics on the brain by a study of the potential changes they produce.

METHOD AND RESULTS

Effect of ether on form of axon potential. The effect of ether on the form of the axon potential was investigated for the alpha group and also for single fibers. In one series of six experiments, potentials evoked by stimuli just above threshold for the alpha fibers were recorded from frog sciatic nerve 1 mm. from the point of stimulation. The stimulating electrodes were connected into one arm of a Wheatstone bridge to eliminate large escapes of current into the leads. The cathode ray oscillograph in association with an amplifier was used as a recording mechanism. The potentials were made monophasic by crushing under the grid electrode and applying 2 per cent cocaine. Three per cent ether or 10 per cent nembutal dissolved in frog Ringer's solution was applied to the region of vertically placed recording electrodes by a drip method.

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FIG. 1. Records of single axon potentials. 1 before application of the anesthetic. 2 and 3 after application of anesthetic. 4 after subsequent washing with Ringer's solution. Time in milliseconds. Note that there is no essential change in duration from the effects of ether or nembutal but in each instance a gradual diminution in area. On washing with Ringer's solution recovery is evidenced.

In all instances these changes lowered the spike potential of the alpha fibers with no increase in duration and with a decrease in area. After definite depression of the potential was evident, washing with Ringer's solution led to recovery of the potential. The negative after-potential is progressively lowered by ether and by nembutal.

In another series of six experiments, the effect of ether and of nembutal was studied in frog nerve on single axon responses made monophasic by crushing and cocainizing under the grid electrode. The preparation extended from the root region to the distal part of the tibial nerve. The stimulating electrodes were applied to the root and the recording electrodes to the fine distal part of the nerve. The drug was applied to the region of the recording electrodes. After definite depression of the potential was evident, washing with Ringer's solution was performed.

Ether and nembutal depress the amplitude of individual axon spikes without changing their duration other than is attributable to internodal delay (Fig. 1). Only A fibers were investigated but all our previous studies indicate that the other fibers would be similarly effected. Blair and Erlanger (1936) have reported similar findings for ether. They state that ether and cathodal polarization produce a block with the same general characteristics.

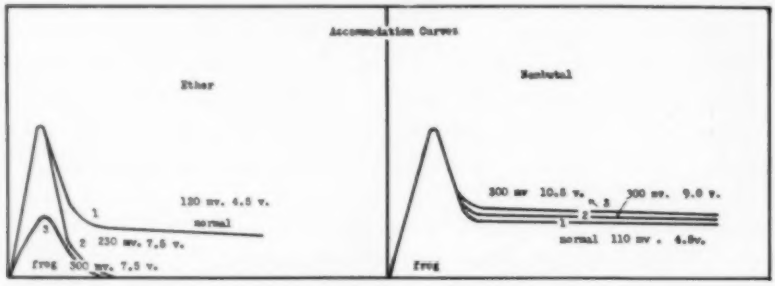

FIG. 2. A. Curves showing the relative amplitudes of nerve fiber responses to faradic shocks superimposed upon a subrheobasic cathodally polarizing current at various instants (abscissa) following its onset. The fall of the curves from their peaks is determined by the ratio and amount of accommodation. Curves of results of an experiment on a green frog sciatic nerve. In all curves MV indicates the voltage of the just subrheobasic current used; V, the voltage applied to the condenser (0.001 mfd.) for the shock stimulus. (1) Response height in millimeters at various instants after start of polarizing current for nerve before use of ether. R 120μV. V 4.5. (2) Response height after 2 minutes washing with 3 per cent in Ringer's solution. R 230μV. V 7.5. (3) Response height after 3 minutes further washing with ether. R 300μV. V 7.5. Interelectrode distance 9 mm. Conduction distance 15 mm. Silver-silver chloride electrodes used.

B. The curves of results of similar type of experiment on green frog sciatic nerve, 5 per cent nembutal in Ringer's solution used instead of ether. (1) Response height before application of nembutal. R 110μV. V 4.5. (2) Response height 11 minutes after application of nembutal. R 300μV. V 9.0. (3) Response height 9 minutes later. R 300μV. V 10.5. Note that ether increases accommodation, nembutal decreases it slightly.

Effect on fiber groups. The effect of ether and nembutal on nerve fiber groups was investigated in six turtle vagus nerves. This nerve yields, after conduction, recognizable A, B, and C potentials. The drugs were applied by the drip method to the region of the recording electrodes. Condenser discharges served as stimuli. It was found that the C fibers were first blocked, then the B fibers, and finally the A fibers. The A fibers recovered first, then the B fibers, and finally the C fibers.

Effect on electrical threshold, absolutely refractory period and conduction rate of fibers. The effect on electrical threshold and absolutely refractory period was determined on frog

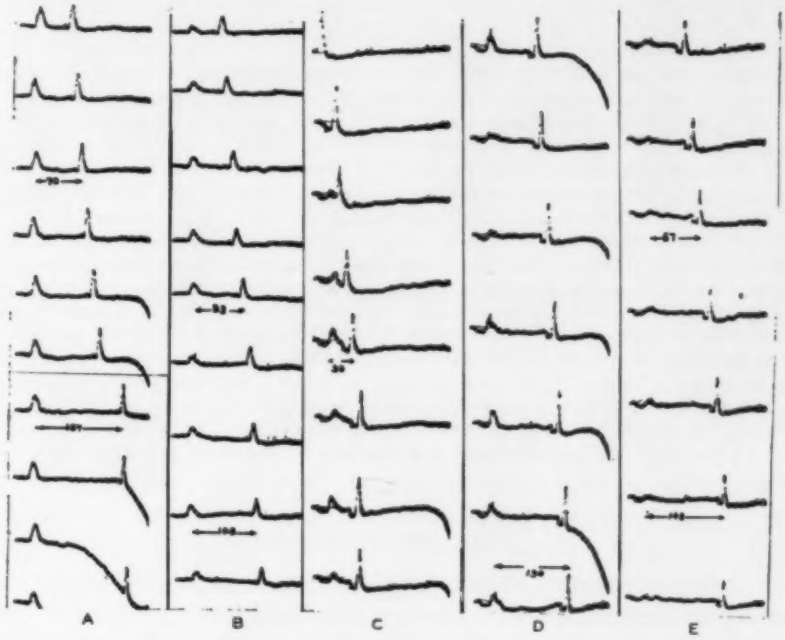

FIG. 3. Records showing the postganglionic responses from paired stimuli to the preganglionic stretch of the superior cervical sympathetic ganglion of the turtle before and after the application of ether or of nembutal to the ganglion by the drip method. Both stimuli are submaximal for the B wave, the second being greater than the first. Column A, records before ether; B, after 3 per cent ether; C and D, records from another preparation before nembutal; E, after 3 per cent nembutal. The size of the response for the second shock varies as the interval of separation between the first and second is altered. Ether and nembutal shorten the period of recruitment as evidenced by the change in the interval of 70 to 167 msec. to 83 to 108 msec. and of 30 to 130 msec. to 67 to 142 msec., respectively, during which time the response to the second shock with paired stimulation is greater than the response to the second shock alone. Characteristically, recruitment begins earlier with ether than in the normal state and later with nembutal. The amount of facilitation under anesthesia is less than in the normal state.

nerves by applying ether or nembutal (5 per cent) to the stimulating electrodes; the effect on conduction rate of the alpha fibers by applying them to the nerve trunk between the stimulating and recording electrodes. From the onset of any recognizable effect of either anesthetic there occurred an elevation of the electrical threshold, a prolongation of the absolutely refractory period and a slowing of conduction. There was no evidence of any excitatory effect. Blair and Erlanger (1936) have presented evidence that the relatively refractory period of the axon is also prolonged by ether.

Effect on accommodation in nerve fiber. The effect of ether and nembutal on accommodation was investigated in green frog sciatic nerves. Only fresh nerves were used because it

was found that preparations soaked in Ringer's solution for several hours sometimes failed to accommodate to cathodal polarization to a normal degree. The drugs were applied in the region of the stimulating electrodes. In one series of 10 experiments a cathodally directed polarizing current, adjusted before each series of observations to be just subrheobasic in intensity and of 200 msec. duration, was applied once a second. A condenser shock (0.001μF. delivered through 35,000 to 40,000ω resistance), of a strength just adequate to yield a response 20 to 30 mm. in amplitude at the point of maximum effectiveness of the two stimuli, was superimposed through the same electrodes at various times during the flow of the polarizing current. The height of the response to the shock stimulus at the various intervals throughout the flow of the polarizing current was marked on translucent paper placed over the face of the oscillograph. This permitted a series of readings to be made very rapidly, thus eliminating as much as possible changes in the state of the nerve with time. By this method response height, not threshold, is measured for accommodation. While not ideal, because response height is an "S" curve against voltage, the error introduced is not great. Readings were made on both normal and anesthetized nerves.

Ether produced a definite increase in accommodation, nembutal a slight decrease (Fig. 3), and washing with Ringer's solution restored accommodation to normal. In another series of four experiments for each anesthetic agent, the strength of polarizing current used was that found just subrheobasic for the nerve in its normal state. This was done because it had previously been noted with strychnine (Heinbecker and Bartley, 1939) and it was again noted with ether that there is no constant relationship between a threshold change to a shock alone and a change in accommodation. With strychnine, a marked decrease in accommodation can be effected with the threshold for a condenser shock either lowered or raised. With ether, a marked increase in accommodation can be effected with no change in shock threshold. In normal nerve that the degree of accommodation increases with an increase in strength of the polarizing current (Blair and Erlanger, 1938). Since ether increases accommodation markedly, while nembutal decreases it slightly, the change in accommodation is not simply the effect of the polarizing current which is progressively elevated, to be kept just subrheobasic, as the shock threshold increases with increasing depression.

Effect on peripheral synapse

The excised superior cervical ganglion of the turtle was chosen for study of conduction through a peripheral synapse because it maintains relatively normal function for a considerable time after excision. It has a preganglionic stretch of 20 to 30 mm. and a long postganglionic one of 40 to 60 mm. Ether and nembutal (5 per cent) were applied by dripping onto the ganglion. Condenser discharges were used to stimulate and the electrical postganglionic responses recorded.

In six experiments with each anesthetic, conduction through the ganglion was progressively blocked. Because observation was continuous throughout the application of the agent, in effect all possible concentrations were observed. With stimuli placed two seconds or more apart there was never evidence of any increase in the submaximal potential area recorded from the postganglionic stretch. Ether blocked the ganglion in a few minutes and recovery was rapid on washing with Ringer's solution. Nembutal, in the concentration used, blocked the ganglion 5 to 10 times more slowly than ether and recovery from it was also much slower.

The same preparation served for studying latent addition (summation interval) and facilitation, as evidenced by recruitment. Paired brief stimuli, submaximal for the B wave but with the second always greater than the first, were applied to the preganglionic stretch and a monophasic record of the postganglionic responses secured. The maximum interval between

stimuli during which the area of the first and second response *together* was greater than the area of the second response alone measured the duration of latent addition; and the much longer interval during which the area of the second response when preceded by the first was greater than the area of the second response alone (recruitment) measured facilitation.

Latent addition averaged 2.2 to 2.5 msec. and facilitation was present from 50 or 70 msec. until 100 msec. Between the two there was a period of relative refractoriness or depression (Fig. 3). After the application of ether or nembutal (3 per cent) the period of latent addition was progressively shortened. By the time that the area of responses was depressed about 50 per cent, the period of latent addition was shortened approximately 50 per cent by ether and to a somewhat lesser degree by nembutal. The period of facilitation was markedly shortened by ether, to a lesser degree by nembutal. The amounts of latent addition and of facilitation are also lessened progressively by both drugs.

Effect on ganglion cells of median nerve cord of Limulus polyphemus. In 20 preparations, ether and nembutal (5 per cent) were applied to the isolated nerve cord of *Limulus*, or to the nerve cord left *in situ* on the excised active heart, or to the nerve cord *in situ* in the body after removal of a narrow strip of the carapace above it. In the later two types of preparation the effects observed are considered to represent primarily the action of the anesthetic agents on the nerve tissue and not on the heart muscle. *Limulus's* heart is neurogenic, and the validity of the above assumption is indicated by the fact that direct electrical stimulation of the heart muscle was still effective after application of the anesthetics to the nerve cord and surrounding heart muscle had abolished spontaneous activity. Further, the potential derived from the nerve cord precedes appreciably the muscle potential. The duration of the potential of the nerve elements varies directly with the duration of the contraction.

Ether, in 6 good excised preparations, increased the frequency of the ganglionic discharges, indicated by heart rate and the areas of the potentials associated with nerve and muscle responses (Fig. 4). In some preparations *in situ* the heart rate decreased for a brief period and then, with slightly increasing anesthetization, it increased. This increase persisted until the potential area associated with each burst of activity fell practically to zero. Similar results were obtained when the heart was left *in situ*.

With nembutal (Fig. 4) there was at times an initial acceleration followed characteristically by a slowing. Associated with the slowing there was an increase in responsiveness, indicated by the potential area, when the heart was left *in situ* and with a maintained blood supply; but such an increase was usually not observed in excised preparations. With still deeper anesthesia the usual and typical effect was a decreased frequency of ganglion cell discharges, *i.e.*, of heart rate, with a gradual decrease in area of the potentials associated with nerve and muscle activity. When the normal coordinated rhythm of the system had broken down, isolated units could be seen to discharge separately at similar frequencies.

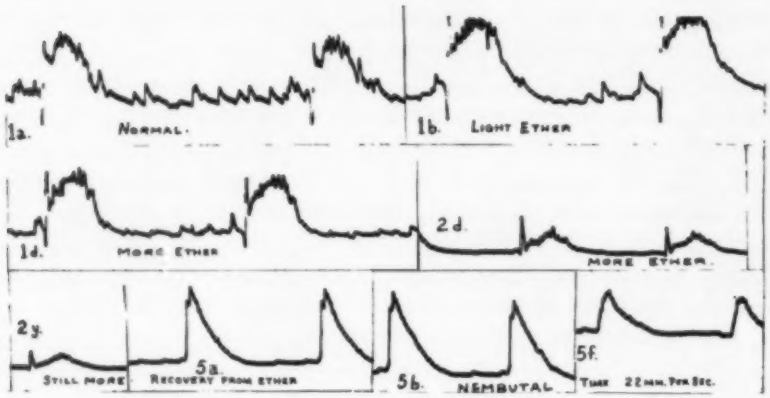

FIG. 4. Records of potentials from the excised median nerve cord and muscle of the heart of Limulus. One needle electrode placed in the tissue close to the median nerve cord, the other at a distance of 2.5 cm. on killed muscle. 1a, normal response; 1b, 1d, 2d, 2y, responses after application of 3 per cent ether in sea water by dripping it onto the median nerve cord. Note in 1b an increase in size of the response with increase in heart rate. 1d, 2d, and 2y show progressive diminution in the size of the response but the increase in rate becomes progressively greater. 5a, the response after recovery from ether by washing with sea water. 5b and 5f, the responses after application of 5 per cent nembutal. Note in 5b a slight increase in the size of the first response after nembutal with an increase in the frequency of the heart rate. In 5f, the typical slowing of the heart with a diminution in response is shown. Time—22 mm. per sec.

Recovery from ether was readily effected with Ringer's solution with a reversal of the depression effects. Recovery from nembutal was always much slower and frequently not complete during one to two hours of observation.

Effect on spinal cord. The effect of these agents on spinal cord activity in the turtle was studied by recording the reflex response of a muscle to a fixed stimulus. In 8 preparations the cord was exposed and transected at the junction of the middle with the distal third. The sciatic nerve on one side was exposed and stimulated with a current just strong enough to yield a good crossed flexion response, the magnitude of the contraction being

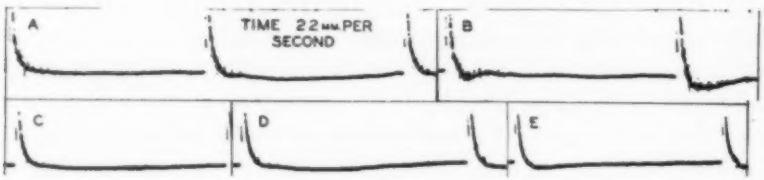

FIG. 5. Records of response from the left quadriceps muscle of the turtle using needle electrodes on stimulation of the right sciatic nerve at 4 second intervals. Cord transected at junction of middle with distal third. Blood supply probably not greatly interfered with. A, normal response. B, response after application of 3 per cent ether in frog Ringer's solution to cord surfaces. Note the increase in number and frequency of the individual responses and the increase in size of the contraction. C, D and E, records after further application of ether. Note decrease in number and frequency of the individual responses with a decrease in the size of the contraction.

measured with 2 needle electrodes inserted into an active thigh muscle. Ether (5 per cent) and nembutal (5 per cent) were applied to the exposed cord below the level of section.

Ether (Fig. 5) led, first, to an increase in reflex activity, as evidenced by increased frequency of individual potentials and increased total area of the electromyogram. This phase was followed by a decrease in frequency and in total area. Nembutal sometimes produced a slight transient increase in frequency and total area of the muscle potentials, though never so marked as with ether, and then regularly led to depression. Washing away the ether

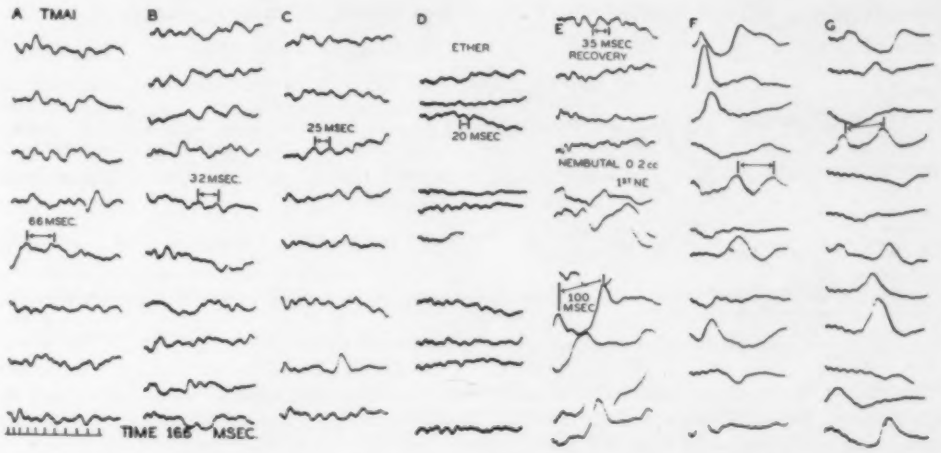

FIG. 6. Record showing the spontaneous activity of the sensorimotor cortex under 3 conditions: A, normal; B, with 3 cc. of ether injected into airline; C, with additional 3 cc. of ether; D, with 4 more cc. ether. Upper records of E after partial recovery from ether, lower records after a first injection of 0.2 cc. nembutal (1 per cent). F, somewhat later. G, still later. Although the waves exhibited are of several frequencies one type of wave can be picked out and followed in the different states of the animal. In A the period between such wave crests is about 50 msec.; in B, 32 msec.; in C, 25 msec.; in D, 20 msec. Recovery in E returns the period to 35 msec. Nembutal quickly shifts the period to about 80 to 100 msec. Time 16.6 msec.

led to fairly complete recovery, in 5 to 15 min.; recovery from nembutal was slow and still incomplete after 1 to 2 hours.

Effect on cortical potentials. The effect of ether, used as a general anesthetic, on the activity of the sensorimotor cortex is shown in Fig. 6. There is a definite increase in the frequency of the normal waves. Occasionally the area of the potentials is slightly increased at the very onset of anesthesia. Nembutal anesthesia slows the wave frequency and at first increases the wave area, with frequent spindle formation (Fig. 6 and 7). With increasing concentrations of either drug the area of cortical potentials is gradually decreased.

In the early stage of ether anesthesia, the electrogram, recorded from electrodes placed deeply in the mid portion of the thalamus is increased and

this increase persists when the cortical activity is already becoming depressed. With deeper anesthesia the thalamic potentials are also decreased. This early increase cannot be regarded entirely as a release phenomenon due to cortical depression, because it occurs on both sides of the thalamus even when one cortical hemisphere has been removed before the start of anesthesia. Under light nembutal anesthesia, there is an increase in area and a decrease in frequency of potentials from the thalamus and basal ganglia.

The immediate cortical response to stimulation of the isolated saphenous nerve is a series of waves in the sensory area (Fig. 8 and 9; ether or nembutal anesthesia). When needle electrodes are used, with grid superficial and

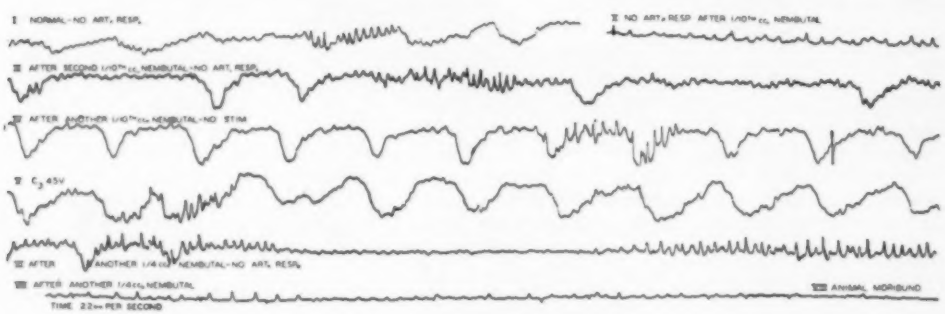

FIG. 7. Records of potential activity of sensori-motor cortex after tetra-methyl-ammonium iodide (designated as normal) to show the effect of progressively increasing nembutal anesthesia. Records IV and V show large waves which have the frequency of the artificial pulmonary ventilation. They may be artefacts but such large waves are at times the result of afferent stimuli developed by the respiratory movements. Record V shows no effect from strong stimulation of the saphenous nerve once every two seconds even though the cortical waves are well sustained. Note the progressive lowering and slowing of the alpha waves especially in record VII & VIII. Time 22 mm. per sec.

ground lead 2 to 3 mm. deep, the rising phase of the first wave ($alpha_c$) is surface positive and reaches a crest 8 to 10 msec. after the shock to the nerve. Its negative phase fuses with the second wave ($delta_c$) which is negative and has a crest time of 40 to 50 msec. A third positive wave follows with a crest time of 120 to 140 msec. When stimulus to the saphenous is strong enough to excite the C fibers, there follows a third negative wave (C_c), with a crest time of 400 to 500 msec., and a positive wave with a crest time of 1100 to 1200 msec. (Fig. 9). Assuming a conduction distance of 0.5 meter, and a synaptic delay of a few msec., the crest times of the $alpha_c$, $delta_c$, and C_c waves are such as would result from conduction in fibers at rates about 80, 20, and 1.2 meters per sec., respectively. These values definitely associate the cortical waves with the alpha, delta (B_1) and C fibers of the cat's saphenous nerve (Heinbecker, Bishop and O'Leary, 1936).

The origin of the potentials which constitute the immediate response cannot be definitely stated. The duration of the waves is consistent with the interpretation that they represent summated fiber potentials. If so, their

quick depression by light anesthesia at a time when spontaneously active elements in the cortex are little effected would indicate that the afferent fiber pathways below the cortex are quickly blocked. If they represent, as well, potentials of cortical interneuron elements, then the latter probably constitute by far the major portion of them.

Gradually deepening ether or nembutal anesthesia depresses slowly the amplitude and area of the three waves. The third wave is depressed most rapidly, the second somewhat later, and the first wave last. Under light surgical anesthesia the third and second waves are gone while the first remains one-half to one-third its normal size. As these late waves are depressed, there is a coincidental elimination of the more general changes in cortical activity which normally follow stimulation of the saphenous nerve, especially of its slower fibers. The findings fit well with the known order of dis-

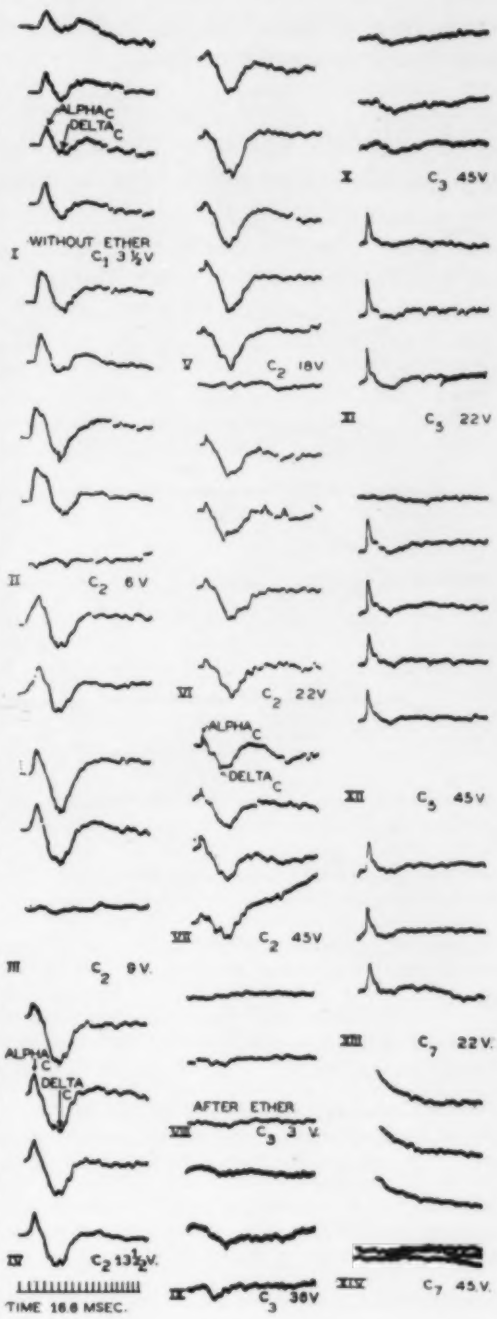

FIG. 8. I–VII, records of the earlier waves of the immediate response of the sensorimotor cortex to increasing strengths of condenser shocks applied to the saphenous nerve. Note a short first surface positive wave, alpha$_c$, with a crest 8 to 10 msec. from the start, followed by a surface negative wave with a crest at 40 to 50 msec., delta$_c$. This wave is probably superimposed upon the negative portion of the first wave. A third surface positive wave with a crest at about 150σ is seen. Records VIII to XIV show the effect of ether on this portion of the immediate response. Note the depression of the waves most marked on the late part of the response and least on its early part. Due to time relationship after the shock, the alpha$_c$ and delta$_c$ waves are in whole or in part regarded as at least the expressions of activity in afferent fibers corresponding to those giving rise to the alpha and delta waves of the conducted saphenous nerve potential. C_1 0.001; C_2 0.005; C_3 0.01; C_5 0.005; C_7 0.1 μ F. Time 16.6 msec.

appearance of sensibility under ether anesthesia, pain sense being lost first and touch and pressure last.

Effect on facilitation in central nervous system

Facilitation was determined in the cat under the influence of tetramethyl-ammonium iodide because anesthesia was found to depress it. Two

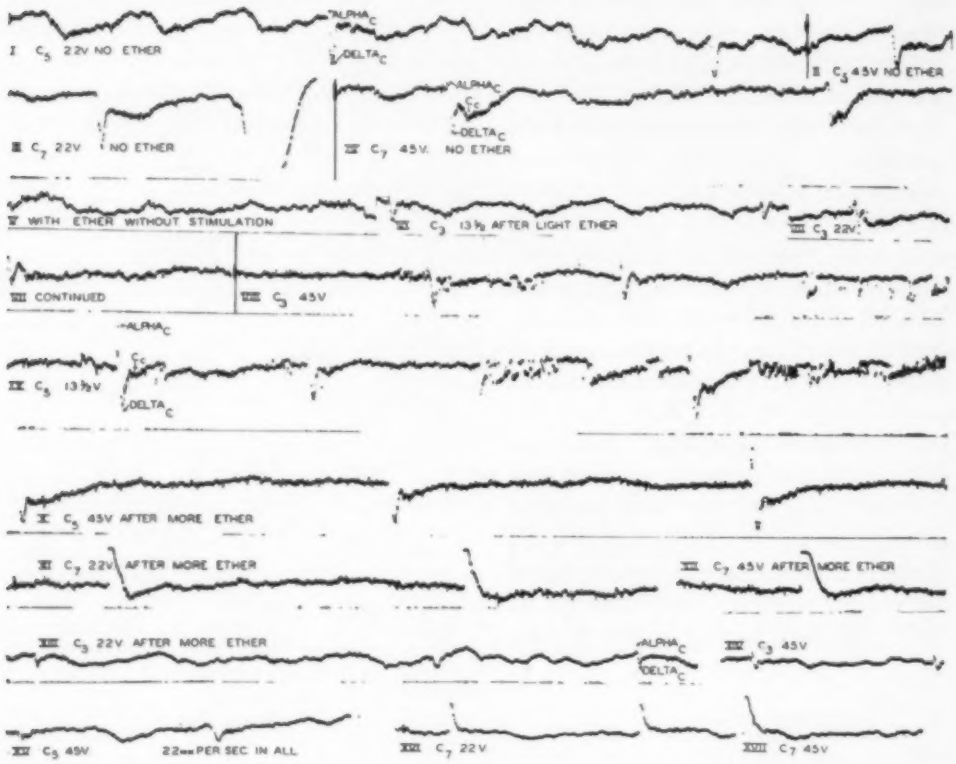

FIG. 9. Records of potentials from sensori-motor cortex to show the immediate response to saphenous nerve stimulation and the effect of ether on it when condenser shocks adequate to stimulate C fibers are used. C_5 13.5 V just above thresholds, C_7 45 V supramaximal for the C wave. Note the increase in area of the immediate response with increasing shocks in records I, III, and IV. In record IV the first wave, alpha$_c$ referred to in Fig. 8, is not recognizable except as a slight brief upswing of the line and is mixed with the shock escape. Its crest time is 8 to 10 msec. Wave delta$_c$ has a crest at 40 to 50σ after the shock and wave C_c at 400 to 500 msec. The values are what would be expected from fiber pathways having an approximate velocity from 80, 20, and 12 meters per sec. if a conduction distance of 0.5 meter and a few sigmas for synapse time are assumed. These are reasonable figures for the speed of the cat saphenous alpha, delta, and C waves. The effect of ether is shown in record VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, & XVI. It depresses the third wave most, the second somewhat less, and the first wave least of all.

nearly equal submaximal stimuli at varying separation were applied to the saphenous nerve (giving alpha plus delta waves) once every 2 sec. and the immediate cortical responses recorded from the sensorimotor area. At a

separation interval so great that the period of relative refractoriness of the direct fiber pathway could not play a role, the size of the second response was increased if preceded by the first stimulus. The second response area is difficult to observe accurately until the stimulus interval is about 100 msec., then it increases gradually to a maximum at about 200 msec. The area of the facilitated second response is greater than that of the second response alone for a period of 80 to 100 msec. (period of facilitation as evidenced by recruitment) (Fig. 10). Spontaneous variations in form and magnitude of the general cortical potentials and a rhythmical rise and fall in the magnitude of the immediate response make it difficult to define with accuracy the amount and the duration of the period of recruitment or to

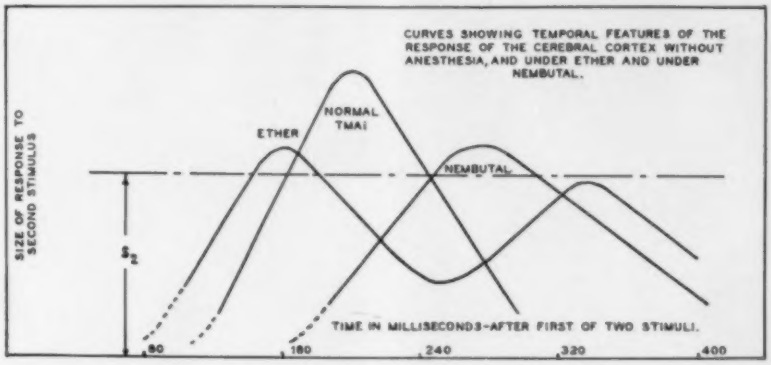

FIG. 10. Curves depicting the size of the cortical response from the sensori-motor area to the second of two nearly equal stimuli to the saphenous nerve submaximal for the whole nerve trunk, nearly maximal for the alpha and delta waves under tetra-methyl-ammonium iodide (TMAI in figure), under light ether and light nembutal anesthesias. S indicates the relative maximal size of the response to the second stimulus alone during the excitability cycle. Note that the second response is visible earliest under ether and latest under nembutal, indicating an earlier recovery of excitability under the former. The amount of facilitation as measured by recruitment is greatest under tetra-methyl-ammonium iodide. It is lessened by ether and nembutal. Time in msec.

observe accurately the instant at which a second response appears. Under tetra-methyl-ammonium iodide increasing ether anesthesia progressively shortens the period of recruitment and decreases its amount; nembutal shortens it less and decreases its magnitude less. The second response is observable earlier under ether than under tetra-methyl-ammonium iodide and later under nembutal. It is of interest to note that the crest times of the periods of recruitment under tetra-methyl-ammonium iodide, ether, and nembutal, 200, 150, and 250 msec. respectively, indicate that facilitation is developed on a cycle of excitability similar to that which determines the frequency of the alpha rhythm. The alpha frequency under these same drugs is 5, 6, and 4 per sec., respectively. The site at which facilitation occurs is not localized by these experiments; probably it is in the nerve cells of the afferent pathway and the first cortical interneuron cells.

In good preparations, without anesthesia, stronger stimuli applied to the saphenous nerve at regular intervals of 0.5 to 0.3 sec. lead to increase in the magnitude of successive immediate cortical responses. This may be regarded perhaps as another type of facilitation. It is associated with a widespread increase in cortical activity, hence it is probably not an expression of events limited to a particular unitary system within the nervous system. Ether and nembutal depress this type of facilitation rapidly.

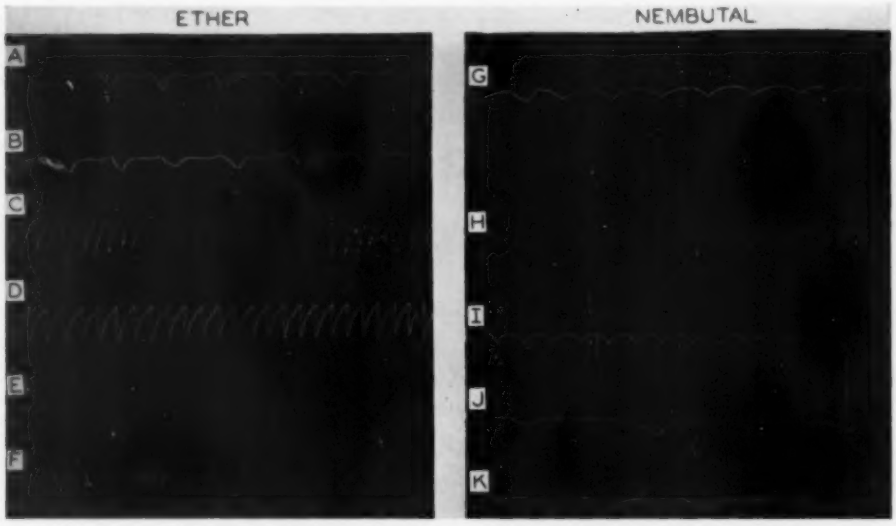

FIG. 11. Chest pneumograms to show the effect on respiration of 10 per cent ether in normal saline administered intravenously to a normal dog. A, normal; B, C, D, E, records showing chest movements under progressively deepening anesthesia. In B is noted a slowing of respiratory rate. It is considered to be an expression of release of the respiratory center from afferent vagus influences. C and D show the excitatory effects of ether. In E anesthesia is very deep but there is no slowing of respiration. F shows the effects of some degree of asphyxia. G, record of another normal dog. H, I, J, and K, records to show effect of 10 per cent nembutal administered intravenously. Note in H an increase in the rate and depth of respiration. I, shows a lessening of these effects. In J and K, slowing of respiration is well established. Note the prolongation of inspiration. Downstroke inspiration.

The existence of a cycle of excitability in the cortex was first demonstrated by Bishop (1933) when he noted that shocks of constant value elicited a variable cortical response unless the rate of stimulation was properly adjusted. This rate in the rabbit was some multiple of 5 per sec., the frequency of the alpha rhythm for this animal. Bartley (1936), using paired maximal stimuli to the optic nerve, plotted the size of the cortical response to the second shock as the interval between shocks was varied. When they were close together (but beyond 20 msec.) the response to the second was absent, with increasing separation it increased in size to a maximum at an interval of 180 to 200 msec., the period of the alpha rhythm under the conditions of the experiment.

Effect on phrenic discharge. Cats were vagotomized and the distal part of a phrenic nerve freed for potential recording under local anesthesia with tetra-methyl-ammonium iodide and artificial ventilation. The animal was then slowly anesthetized with ether or nembutal and changes in the phrenic discharge followed. In dogs the respiratory movements were recorded with a pneumograph applied around the chest and the anesthetic was administered in 10 per cent concentration in Ringer's solution intravenously. It was thus possible to record the typical action of the respiratory mechanism of the intact animal and the effect on it of these anesthetic agents.

Ether (Fig. 11) first increased the frequency and amplitude of the response, sometimes after a transitory slowing without much change in amplitude. The increase in rate persisted as inspiration was gradually depressed by deepening anesthesia. Only in the terminal stages was the respiratory rate slowed. Nembutal (Fig. 10) led to a transitory increase in the frequency of respiration with a slight increase in the depth of inspiration, which was soon followed by marked slowing of respiration and depression and slowing of inspiration which progressed with depth of anesthesia.

Phrenic nerve potentials showed similar changes in the frequency of discharge and the duration of the discharge process. The increase in amplitude of inspiration during the excitatory stages was associated with an increase in frequency of the individual potentials comprising the total potential record, and slowing of inspiration with a decrease. It has been previously shown that the discharge lasts throughout inspiration (Heinbecker, 1937) and that the individual nerve fibers to inspiratory muscles are active approximately throughout this period (Bronk and Ferguson, 1935).

The results show a striking difference in effect of the two anesthetic agents on the respiratory center; ether increases the frequency of its discharge while nembutal decreases it. Ether, during light anesthesia, is much more an excitant than is nembutal.

Analysis of Results

Before interpreting the potential changes in the central nervous system resulting from ether and nembutal, it is necessary to state our views based on the work of this laboratory concerning the nature of synaptic and nerve cell activity and as to the source of the potentials recorded from the cortex and spinal cord.

In the median nerve cord of *Limulus polyphemus* a long sustained simple potential (Heinbecker, 1933), on which are superimposed small individual potentials having the duration of axon spikes, is associated with activity in a large pace-maker ganglion cell. Potentials of this type were recorded from short masses of ganglionic tissue in which only a single pace-maker cell was shown to be present by the examination of serial sections of the tissue while preparations without such cells failed to yield the large long potentials. The pace-maker function or autochthonous rhythmicity of these ganglion cells has been established beyond question by Carlson (1909),

Hoffmann (1911), and Heinbecker (1933). Further, the duration of the period of activity of the fibers and frequency of the individual axon spikes varied directly with the amplitude and duration of the long sustained potentials with which they were associated. The cell response can be modified both as to rate and magnitude; and, other conditions remaining the same, the potential area decreases inversely with the frequency.

On the basis of such evidence from *Limulus* it is inferred that spontaneously rhythmic nerve cells in the mammalian cortex are mainly responsible for the long sustained potentials observed in the electroencephalogram. Similar long potentials recorded from the spinal cord after extrinsic nerve stimulation are interpreted as due to the prolonged depolarization of interneuron and anterior horn cells produced by synaptic stimulation. This view is shared by Eccles (1939). Nerve cells of the type found in the superior cervical sympathetic ganglion do not give rise to long potentials of any appreciable magnitude. Their activity would then not be expected to be associated with repetitive axon discharges. That they are not, was early established by Heinbecker (1930) in the turtle and by Bishop and Heinbecker (1932) in the cat.

Blair and Erlanger (1939) demonstrated that the action potential of a fiber can be made to stimulate across a non-responding gap of one or two internodal segments. It seems reasonable to assume that the fiber action potential could stimulate across the gap of a dendritic or cell body type of synapse in a similar manner. The effectiveness of synapse stimulation would then depend upon the strength of the axon action potential, the electrical conductivity of the synapse medium, and the electrical excitability of the structure beyond the synapse. The available evidence indicates that the effects of the axon action potential across the synapse are at least two, one of brief duration measurable as the period of latent addition, and a second of much longer duration (maximum at 200σ for the A fibers in the sensorimotor region of the cat and 100σ for the B fibers in the cervical sympathetic ganglion of the turtle) measurable as the period of recruitment. In the nerve fiber both processes have been intensively studied, the first as the period of latent addition, the second as the period of super-normality. The period of recruitment here measured has the time characteristics of the slow after-potential recorded from the sympathetic ganglion by Eccles (1937). The period of facilitation for the central nervous system now reported has time values more like those of after-potentials than of spike potentials. We suggest that the potential recorded from the *Limulus* ganglion cell is associated with a process similar to the one responsible for the sympathetic ganglion cell negative after-potential, the magnitude and duration of which are reflected in the magnitude and duration of facilitation.

Inhibition of the nerve cells by ether and by nembutal is similar to inhibition of the pace-maker ganglion cells of the heart of *Limulus* by extrinsic inhibitory nerves, at least in that both result in a depression of that potential assumed to be associated with the cell response. In this prepara-

tion, acetylcholine depresses the potentials much as does stimulation of the extrinsic inhibitory nerve fibers. Ether, which increases accommodation in the axon shortens the cell response, while strychnine which decreases accommodation in the axon lengthens the cell response (Heinbecker and Bartley, 1939). Nembutal, which decreases accommodation to a slight extent, acts like strychnine before it depresses appreciably. To support a suggestion that nerve cell inhibition may be effected through a process similar to that resulting in increased accommodation in the axon is the demonstration by Gilson (1939) that stimulation of the turtle vagus increases accommodation of the heart muscle and markedly shortens its response. It is possible that accommodation is an expression of the chemical reactions of the "activity or response substance" on which an excitatory or inhibitory substance acts; for we have shown that there is no constant relationship between a change in initial shock threshold and a change in accommodation.

Some workers have suggested that inhibition, as such, may be associated with the development of a positive potential. No evidence of this has been found during studies of the *Limulus* heart cord in depression. A reversal in potentials does occur but is always due to an unequal depression at the vicinity of the recording electrodes. The cyclic change in cortical excitability and responsiveness is, however, associated with potential variations.

The actions of ether and of nembutal on the various preparations used indicate that depression of the intact nervous system probably is the result of a depression of activity in axons and in the dendrites and somata with which they synapse. These drugs depress the early and late excitatory processes and the response process in both fiber and cell. Depression of the axon is shown by a lowering of the axon spike potential and the negative after potential. The electrical threshold of a nerve trunk is raised, the absolutely and relatively refractory periods of its fibers are prolonged, and the conduction rate is slowed. The smallest fibers are depressed before the large ones. Depression of the cell excitatory process is indicated by reduction in the amount and duration of latent addition and of facilitation; and of cell responsiveness by a decrease of the slow potentials associated with their response and by a diminution or cessation of activity in their associated axons.

The relative susceptibility to depression of the axons, dendrites, and cells comprising the central nervous system differs. Our results seem to warrant the interpretation that activation through the synapse is eliminated before the responsiveness of the cell beyond is greatly depressed. Spontaneous activity in the cortical cells, for example, is well sustained long after the immediate response to saphenous nerve stimulation is entirely eliminated. Blocking at the synapse might then be the result of a lowering of the action potentials in the fine axon terminations which impinge on the nerve cell or its dendrites. Indirect evidence for this is seen in the slowing of respiration just after ether is administered intravenously in the intact

animal for this change would follow the elimination of afferent vagus impulses. Ether *per se* increases the frequency of response of isolated spontaneously active nerve cell complexes.

Depression of all synapses by anesthetics does not proceed equally throughout the nervous system. It was previously noted by Bishop, Heinbecker and O'Leary (1934) that the ability of afferent vagus stimulation to modify blood pressure was much less affected by ether anesthesia than was its ability to accelerate respiration. Synapses of effector mechanisms (bouton type?) such as those concerned in respiration are relatively unaffected by concentrations of anesthetic agents which completely block synapses of afferent pathways. Cortical potentials are almost completely depressed by ether or nembutal before respiration ceases. The speed of anesthetic action also varies in different regions. It is most rapid in the cortex, slower in the spinal cord, still slower in the basal ganglia and brain stem, and slowest in the peripheral portions of the sympathetic and somatic nervous systems.

Our results indicate that ether, as a depressing agent, modifies the properties of the nerve axon in a manner similar to cathodal polarization (Blair, 1938). The axon spike potential is lowered, the period of latent addition is shortened, the absolute and relative refractory periods are prolonged, and accommodation is increased by both. Conversely, strychnine (Heinbecker and Bartley, 1939), as an excitant, changes the properties of the axon in the same way as does anodal polarization (Blair, 1938).

We have here no evidence concerning particular chemical changes resulting from the action of ether or of nembutal on the nervous system, but presumably these drugs depress the chemical reactions involved in both the excitation and the response processes.

Summary and Conclusions

The actions of ether and nembutal on the nerve axon, the synapse, the rhythmically active nerve cell, the spinal cord, and the brain have been analyzed principally in terms of the action potential changes they produce.

The amplitude and area of the axon spike potential and the negative after-potential are progressively diminished by ether and by nembutal.

The electrical threshold of the axon is raised, its conduction rate is lessened, and its absolutely refractory period is prolonged by ether and by nembutal.

Ether markedly increases accommodation in the axon, nembutal decreases it slightly.

Both ether and nembutal block conduction through a peripheral ganglion. This is interpreted as indicating that they progressively lessen excitation of the soma through the synapse.

With depression by ether or nembutal, the period of latent addition (summation interval) at the synapse is shortened and the effectiveness of temporal summation is lessened. Further, the period of recruitment is shortened by these agents in proportion as they decrease the magnitude of

the cyclic variations in amplitude and area of the immediate cortical response.

Ether increases the frequency of discharge of nerve cells possessing spontaneous rhythmicity and nembutal decreases it, often without any initial increase. Both drugs first increase the magnitude of the response of nerve cells and then, with increasing anesthesia, decrease it. The increase produced by nembutal is considered to be in part a consequence of the reduction of the response frequency.

Ether and nembutal differentially depress the immediate cortical response to saphenous nerve stimulation, the order of final extinction of its constituent waves being third, second, and first. The general cortical excitation produced by spread is eliminated as the late waves are depressed. These effects are interpreted as due to blocking of synaptic stimulation.

The action of ether on the nerve cell or cell group suggests that it first stimulates and then depresses the excitation and response mechanisms. Nembutal has a much feebler preliminary stimulating action. The duration of the cell response under ether is less than that under nembutal, and recovery of responsiveness under ether is more rapid than under nembutal. This may account for the different discharge frequencies induced by these agents.

Present and past researches of this laboratory bearing on the question of excitation and inhibition of neurons are analyzed. The facts suggest that excitation is an effect on the soma produced by the summation of brief electrical stimuli which arrive at the terminals of impinging nerve axons. A brief and a prolonged excitatory state develop in the soma following their action. Inhibition, aside from the well known rhythmical changes in responsiveness, has not been found to be accompanied by the development of a potential. It results in a lowering or elimination of the potentials associated with activity and presumably would oppose the activation of nerve cells.

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DEGENERATION AND REGENERATION OF SYMPATHETIC SYNAPSES

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INTRODUCTION

THE SUPERIOR cervical sympathetic ganglion is an easily accessible part of the nervous system in which to study the form and function of simple synaptic junctions, for as was shown by Bishop and Heinbecker (1932), all impulses passing in by the preganglionic fibers must traverse a synapse before emerging by the postganglionic fibers. Eccles (1936) has stimulated the postganglionic trunk electrically and has been unable to record any transmitted impulse in the preganglionic fibers. He found that all preganglionic impulses suffered delay in passing through the ganglion and concluded that all preganglionic fibers end in synapses on the cells of the superior cervical ganglion. In the present study, histological examinations have been made of the synaptic endings of the normal, degenerating, and regenerating fibers entering the ganglion. These findings have been correlated with the results of parallel electrophysiological observations on these synapses. The histological studies were made with silver stains, and the electrical studies with a cathode-ray oscillograph.

The literature which bears directly on the present work falls into the following three categories: (i) The structure of normal sympathetic synapses. (ii) Experimental degeneration of sympathetic synapses. (iii) Experimental regeneration of sympathetic synapses.

Normal sympathetic synapses. The papers of Smirnow (1890), Cajal (1891, 1893, 1903, 1905), Huber (1899), and Ranson and Billingsley (1918) contain the early and fundamental work on the structure of the synapses in the sympathetic nervous system of normal animals. De Castro in 1923, and Lawrentjew in 1924, contributed further studies and during the past fifteen years they with their associates have brought forward a wealth of information concerning sympathetic synapses.

De Castro (1923) used the silver staining technique of Cajal for blocks of tissue fixed in pyridine and ammoniacal alcohol, and the frozen section method of Cajal (1921) for mammalian ganglia fixed in formalin. His preparations showed the preganglionic fibers approaching the ganglion cells and breaking up into fine fibrils which insinuated themselves between the dendrites and their overlying capsule and finally ended in delicate rings on the perikaryon. Lawrentjew (1924) using a modification of the Golgi staining method found similar structures in the superior cervical ganglion in normal cats and dogs.

Fedorow and Matwejewa (1935) used the Gros-Bielschowsky technique to demonstrate sympathetic synapses in the frog. Preganglionic fibers were

seen to wind spirally around the dendrites of the ganglion cells and to form one or more rings or discs en route, usually at the junction of the dendrite with the cell body. Thereafter the fibril ramified in many different ways, ending in filamentous loops or terminal discs which possibly represented the "growth cones" of the developing preganglionic fibers. Fedorow (1935) has obtained convincing cinematographs of the pericellular terminations of preganglionic sympathetic axones in living preparations of frogs. Insinuated between the nerve cell and its connective tissue capsule minute discs were visualized attached to fine spirally arranged preganglionic fibrils. The capsule was draped over the crater-like hole of the bouton ring as a piece of cheesecloth is placed over the mouth of a churn. Electrical stimulation of the preganglionic fibers *in vivo* caused these boutons to assume brilliant coloration when neutral red was present as an indicator. In the same laboratory Smitten (1937) confirmed the subcapsular position of the synaptic endings, and showed that when the capsule was stretched with microdissecting needles the ring-like boutons under it took the form of ellipsoids.

Stöhr (1935) rejected the neurone theory as applied to the sympathetic nervous system and claimed that there is no interruption of the fiber pathway at the synapse. Nonidez (1937), using stains specific for connective tissue, has been able to stain selectively the "periterminal reticulum" which Stöhr believed to be nervous in nature. Kolossow and Polykarpowa (1935) have shown the presence of this reticulum after preganglionic sympathetic fibers have been destroyed. Lawrentjew (1939) succeeded in reproducing Stöhr's pictures of the "periterminalreticulum" only after immersing fresh material in 30 to 40 per cent formol for fixation. Stöhr and his pupils offered no physiological evidence in support of their thesis, nor have they carried out the elementary degeneration experiments which would prove or disprove the nervous composition of their "periterminalreticulum." The writer, after examining Stöhr's preparations in Bonn, was unconvinced of the nervous nature of the structure there demonstrated as the "periterminalreticulum."

Degeneration of synapses. Waller (1851), Budge (1855), Nikolajew (1893), Tuckett (1896) and Langley and Anderson (1896) were the first to study experimental degeneration in preganglionic fibers and synapses. Waller as early as 1852 remarked upon the "disorganized" state of preganglionic fibers 6 days after they had been transected. Ranson and Billingsley (1918) using the pyridine silver stain, were unable to demonstrate the normally dense intercellular plexus in the superior cervical ganglion of cats once the preganglionic trunk had been divided and had degenerated.

De Castro (1930) carried out a comprehensive research on degeneration in the superior cervical ganglion in more than one hundred cats. He used the block methods of silver impregnation after fixation of young material in hypnotics such as somnifene and chloral hydrate. Seventeen hours after dividing the preganglionic fibers he detected throughout their length, early fragmentation with granular changes, and an increased affinity for silver salts. At 24 hr. the terminals were granular and hypertrophied, and by 36 hr. only a few remained. At 5 days a few resistant fibers could be seen interlacing among the cells, but at the end of the 7th day all had broken down into heavy dark granules. In the 24- and 36-hr. cats a medium shock from an induction coil caused a slight dilation of the pupil. After 48 hr. a strong stimulus failed to evoke any response.

Lawrentjew (1934) used the Gros-Bielschowsky technique in his study of degeneration and regeneration in the superior cervical ganglion in 78 animals, mostly cats. His histological findings and his series of mechanical recordings from the nictitating membrane confirmed the work of De Castro.

Regeneration of synapses. Waller (1853), Schiff (1894), Langley (1897, 1900) and Tsukaguchi (1916), have demonstrated functional regeneration in the sympathetic nervous system at varying periods of time following suture of the divided ends of the preganglionic trunk. De Castro (1930) observed the severed preganglionic fibers regenerating in the cervical trunk within 24 to 72 hours, throwing out a brush of short branches, each ending in a spherical "boule de croissance" or a ring-like "bouton de croissance." Regenerating fibers entered the ganglion within 5 to 12 days depending upon the degree of injury and the distance of the lesion from the ganglion. Eight days after compression or 12 days after division of the cervical trunk close to the ganglion, subcapsular boutons were visible on both perikarya and dendrites of the sympathetic neurones. From 15 to 17 days after division, a medium stimulus caused changes in the pupil and nictitating membrane, which accorded with the arrival of the earliest bouton endings on the ganglion cells. Forty to 50 days after operation many of the ganglia had complete functional and structural restoration.

Lawrentjew (1934) reported progressive stages in regeneration similar to those in De Castro's series, and compared the "growth bulbs" on the regenerating fibers to the spherical endings on the axones of neurones in tissue cultures which Lebedew and Sorin had demonstrated in his laboratory.

MATERIAL AND METHODS

Cats ranging in weight from 1.4 to 3.8 kg. were anaesthetised with Nembutal intraperitoneally. A single incision was made on the left side of the neck to suit the later arrangement of electrodes in the oscillograph room. On reaching the carotid sheath great care was taken in the longitudinal separation of the preganglionic sympathetic trunk and its artery from the vagus nerve. In the average animal the preganglionic trunk was transected 2.5 cm. below the superior cervical ganglion to ensure a sufficient portion of regenerated trunk from which to "lead off" electrically at a later date. In the degeneration studies the preganglionic trunk central to the point of division was dissected out and removed as far down in the thorax as possible, to prevent any confusing regeneration. In the cases in which regeneration was to be studied great care was taken in the approximation of the freshly cut ends of the sympathetic trunk. Two Cushing silver clips were applied longitudinally to the sheaths of the nerve segments, and served to keep the junction clean as well as to make it easy to locate the exact point of section later on.

Electrophysiological recordings were made on the animals following decerebration under deep ether anaesthesia. The cathode-ray oscillograph technique (Eccles, 1935a), was used, the animals being kept in a humid chamber throughout.

The superior cervical sympathetic ganglion and its appended pre- and postganglionic trunks were fixed in 15 per cent formalin (Merck) after the blood vessels had been washed through with warm Ringer solution followed by 5 per cent formalin in Ringer. The addition of 2 to 3 drops of pure pyridine (Kahlbaum) per 10 cc. of fixation formalin improved the quality of the staining in the Cajal and Río-Hortega methods. The optimum fixation time was from 10 days to one month, but sometimes much older material proved satisfactory. In general, the younger animals gave the best histological pictures. When it was desired to store an excess of frozen sections already cut, these were placed in a 5 per cent solution of formalin, and then washed well before using.

After trying many methods for blocks and for frozen sections the following were selected as being the most useful for staining sympathetic boutons:—Río-Hortega's double impregnation method for neurofibrils (1921); Cajal's modification for frozen sections (1921); and the Gros-Bielschowsky method as demonstrated by Fedorow in Lawrentjew's laboratory in 1937. All these techniques and notes concerning their vagaries and peculiarities have been detailed by the author (Gibson, 1937, p. 481).

Experimental Results

Normal superior cervical sympathetic ganglion. Histological examination of the normal superior cervical sympathetic ganglion disclosed synaptic structures similar to those existing in the central nervous system. The two usual forms, boutons terminaux and boutons de passage could be clearly seen. Their number and distribution were, however, very different from those in the central nervous system. The largest number of boutons, of whatever type, seen on one cell and its processes, was thirteen. One microscopic field yielded twenty boutons on focussing, but in the best stained sections the maximum was twenty boutons per hundred cells.

The terminal boutons (Fig. 1) were darkly stained with clear smooth outlines. Some were so large (6μ to 7μ) that they could not be seen completely in one focal plane. The average endings were 2μ to 3μ in diameter. Both circular and angular types were usually seen to be continuous with a very fine fibril. Dendrites as well as perikarya showed boutons in contact with their surface.

Boutons de passage (Fig. 2) were present in normal ganglia in much greater numbers than were boutons terminaux. On the results obtained with the present stains it would seem possible that the boutons de passage are the more important synaptic structures. They occur only on the finest preganglionic fibers and are not to be seen unless these delicate, ramifying filaments have been impregnated. Boutons de passage are definite, darkly stained rings which occur along the course of preganglionic fibers at varying distances from their termination. They enable one fiber to make contact with many different ganglionic cells or even with many different points on one cell. As many as 5 such contacts around the edge of one perikaryon have been seen on focussing.

Normal boutons de passage rarely exceed 2μ in diameter, and on the average they are considerably smaller. In silver slides counterstained with methylene blue, boutons de passage were subcapsular, making direct contact with the perikaryon. Some have been seen as near as 3μ to their terminal bouton. The boutons de passage vary in shape from circular to elliptical, but in the latter case they are always symmetrically tapered.

On a few cells of one normal ganglion some minute, platelet-like structures were clearly visible. They seemed to be confined to the surface of the cells, were elliptical in shape and darkly staining. They had light, though not hollow centers. No neurofibrillar connections could be seen after repeated examinations under the oil-immersion lens. They did not resemble any sort of connective tissue structure; they may represent an abnormal arrangement of the chondrioma of the ganglion cells as described by Ortiz-Picon and Perez Lista (1929).

Degeneration of preganglionic fibers. The earliest observations on de-

generation were made 2 days after dividing the preganglionic trunk 2.5 cm. below the superior cervical ganglion. The preganglionic fibers were deformed and shrivelled, and had an increased silver affinity. The myelin sheath along many fibers was disintegrated into coarse granules. The boutons terminaux were slightly swollen and darkly stained. In some cases the fibril leading to the bouton was not appreciably changed, and in one case a fiber was seen intact after its granular bouton had broken off. Boutons de passage increased slightly in size, and in density of staining.

Two days after operation the action potential spike was normal in shape although a little diminished in size in comparison with that of the ganglion of the unoperated side. This probably indicated that fewer ganglion cells were discharging impulses. There was no significant slowing of the impulse conduction in the preganglionic fibers. The latent period of response to a stimulus was a little longer than normal, possibly indicating a slight lengthening of synaptic delay. As can be seen from Fig. 9a, the S_1 and S_2 components of the spike could be separated.

By the 3rd day of degeneration, destructive changes were further advanced. Some fibers had become fenestrated and hypertrophied, while the heavier boutons were still easily distinguished from swollen or vacuolated fibers. At four and one-half days the resistant fibers were affected over their entire course, and filling in of the rings was seen (Fig. 3). No neurofibrillar changes were seen inside the ganglion cells. Six days after division, the preganglionic fibers were either broken down into granules engulfed in Schwann cells, or were in a swollen and fragmenting state. The fine intercellular plexus of fibers had disappeared, and only a few residual boutons could be seen (Fig. 4).

The preganglionic fibers were inexcitable just distal to the point of section. Nearer the ganglion a few were still excitable, but their threshold was very high. A small discharge was set up from the ganglion, but the spike action potential was only about 2 per cent of normal. It was definitely due to synaptic transmission to the ganglion cells for it was abolished by painting nicotine (1:1000) on the ganglion. The diminished size of the spike shows that the synaptic excitation of only a few ganglion cells was adequate to excite the discharge of impulses. The synaptic delay was 7 to 8 msec., at the shortest, and as long as 15 msec. for some of the impulses transmitted. It was not possible to be sure what group of ganglion cells was still functioning (Fig. 9b).

After 8 days, only granular debris could be seen in and around the Schwann cells where the disintegrated fibers entered the ganglion. No fine fibrils were observed at this stage. Strong electrical stimuli on the preganglionic trunk failed to produce any action potentials in the ganglion cells or in the postganglionic fibers. However, antidromic impulses backfired into the cells via the postganglionic fibers produced normal action currents from the cells (cf. Eccles, 1936). *Thus the ganglion cells themselves were not affected by degeneration of the preganglionic fibers.*

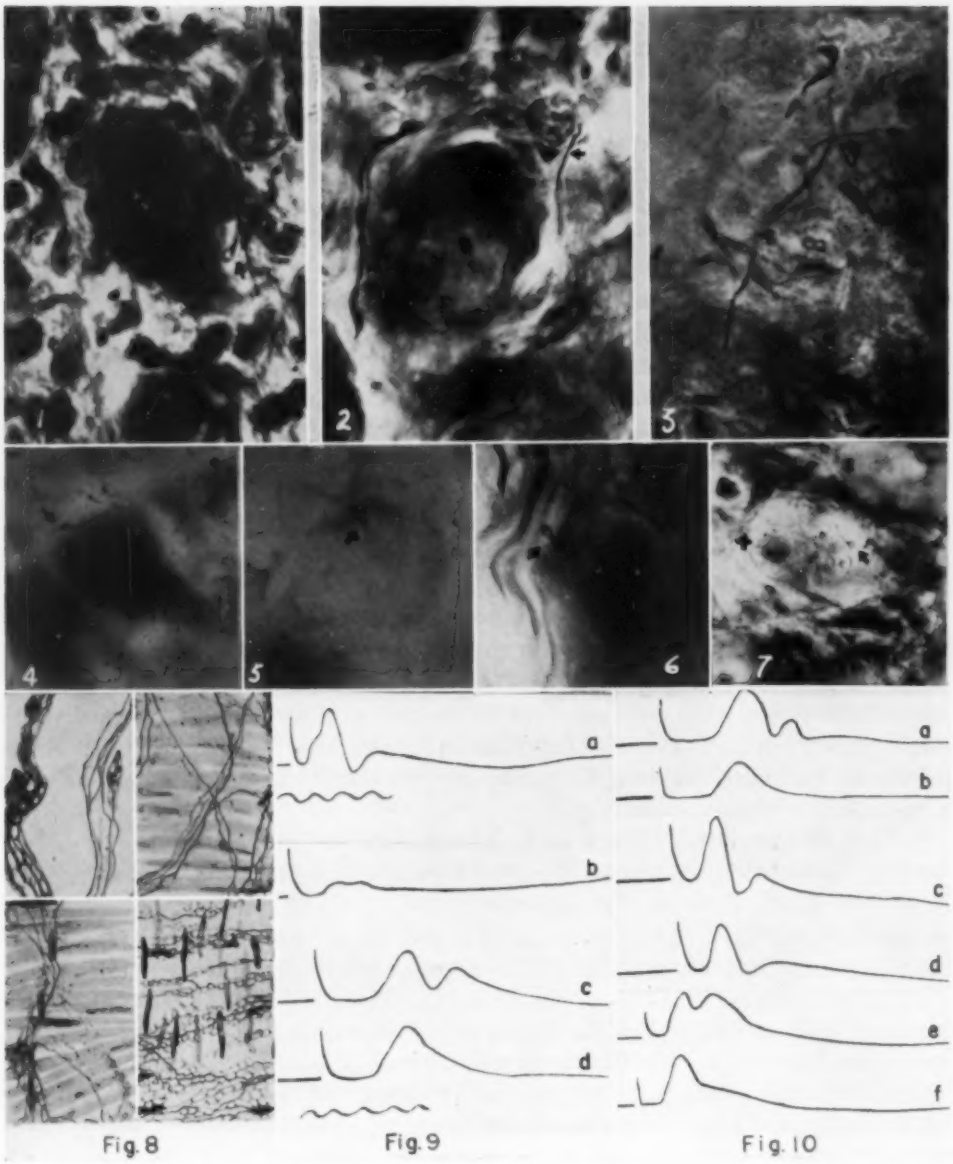

Fig. 8 Fig. 9 Fig. 10

FIG. 1. Terminal bouton ending on cell body in normal superior cervical sympathetic ganglion of a cat. Río-Hortega stain.

FIG. 2. Bouton de passage in normal superior cervical sympathetic ganglion, lying between a neuroglial nucleus and the ganglion cell. Río-Hortega stain.

FIG. 3. Pre-ganglionic fibers 4.5 days after division of the sympathetic trunk. Note the thickening and uneven staining of the fibres, Stain: Cajal's modification for frozen sections.

FIG. 4. Resistant fibre and bouton on the surface of a sympathetic ganglion cell 6 days after section of the pre-ganglionic trunk. Gros-Bielschowsky stain.

FIG. 5. A regenerated terminal bouton on a sympathetic ganglion cell 44 days after cutting the pre-ganglionic fibres. Gros-Bielschowsky stain.

Regeneration of preganglionic fibers. The first signs of regeneration were seen 11 days after the preganglionic fibers had been divided. Thin unmyelinated fibers bearing small loop endings could be seen in the peripheral stump of the sutured preganglionic trunk. These were sharply defined by the silver staining and tunnelled along the old courses between the Schwann cells.

By 14 days there was no recovery of function, and no electrical response of the ganglion cells or postganglionic fibers was elicited by preganglionic stimulation. At 21 days heavy fibers could be seen in the preganglionic trunk at the entrance to the ganglion, but no action potential of the ganglion cells or postganglionic fibers could be recorded on stimulation.

Regeneration of boutons was first seen 44 days after operation. The fine terminal fibrils which had been present in the normal ganglia had returned and had made contact with cells and dendrites after running a sinuous course. Many of the incoming fibers were myelinated distal to the neuroma and into the ganglion itself. Small boutons terminaux and boutons de passage stained darkly and were applied to the dendrites or to the cell body (Fig. 5). No neurofibrillar changes could be seen inside the ganglion cells.

A strong electrical stimulus to the preganglionic trunk between the point of section and the ganglion itself, produced a double spike action potential in the postganglionic fibers. The first spike was very large, and the second was well-formed but small (Fig. 9c, d). A strong stimulus just central to the nerve suture caused a fairly large first action potential spike followed by a small later one. A weak stimulus caused only a single response of medium height (Fig. 10a, b). A strong stimulus applied 31 mm. below the neuroma

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FIG. 6. Terminal bouton on a regenerated fibre making contact with a sympathetic ganglion cell. 70 day cat. Río-Hortega stain.

FIG. 7. A fine regenerated pre-ganglionic fibre ending by means of a terminal bouton on a cell in the superior cervical ganglion 92 days after cutting the pre-ganglionic trunk. A bouton de passage is indicated at the opposite end of the cell. Río-Hortega technique.

FIG. 8. Four figures by Lawrentjew to show the effect of concentrated fixation formol on nervous tissue. The upper two indicate, from left to right, the clear-cut nerve fibres after fixation in 12 and 20 per cent formol respectively. The lower left panel shows the "periterminalreticulum" appearing with 30 per cent formol, while the right shows the reticulum produced by fixing in 40 per cent formol.

FIG. 9. (a) Action potential spike recorded from the superior cervical ganglion 2 days after its pre-ganglionic trunk was divided. The S_1 and S_2 components are visible. (b) Greatly diminished spike (2 per cent of normal) after 6 days' degeneration. Highly amplified. (c) Regeneration in 44-day cat. Action potentials recorded when the pre-ganglionic trunk was strongly stimulated 31 mm. central to the point of division. (d) A weaker stimulus produced a single spike.

FIG. 10. (a) 44-day cat. Action potentials recorded after stimulation of the preganglionic trunk 8 mm. central to the ganglion, and distal to the neuroma. A strong stimulus produced a large spike followed by a small late one. (b) A weak stimulus at the same point as in (a). (c) 44-day cat. Stimuli were applied 17 mm. central to the ganglion (*i.e.*, just below the suture). Two spikes were recorded after a strong stimulus. (d) A weak stimulus failed to evoke the later spike. (e) 92-day cat. Regeneration of the pre-ganglionic fibres. A strong stimulus produced an S_1 spike followed by an S_2 wave. (f) 92-day cat. A weak stimulus produced only the S_1 spike, but the wave remained negative for a considerable period, suggesting a small discharge from S_2 cells.

evoked two large spikes, whereas a weaker stimulus brought out only the first spike (Fig. 10c, d).

The preganglionic trunk central to the point of section conducted impulses at almost normal rates. The part peripheral to the suture, however, had a conduction rate of 1.5 m. per sec. for the fastest fibers, and 1.1 m. per sec. for the average fibers; *i.e.*, less than 10 per cent of normal values. Allowing for this slow preganglionic conduction time the synaptic delay at the fastest ganglion cells (presumably S_1) was not more than 4 msec., which is only a little more than the normal, *i.e.*, 3 msec. The delayed spike which appeared on strengthening the stimulus to the preganglionic fibers was presumably due to the connection made by a group of high threshold regenerated fibers with a group of ganglion cells having a very long synaptic delay. In this case the synaptic delay was as long as 20 msec., and was probably due to S_4 cells.

With a still stronger preganglionic stimulus, either to the undegenerated or to the regenerated sections of the preganglionic fibers, a still later spike appeared in the ganglionic action potential. This was probably due to an even later response of some ganglion cells. Thus, the preganglionic fibers of higher threshold regenerated so as to evoke responses from ganglion cells having longer synaptic delays. This strongly suggests that there has been selective regeneration of the fast, low-threshold preganglionic fibers to cells with short synaptic delays, and of slow, high-threshold fibers to slow cells. The other possibility is that the higher threshold fibers take a longer time to set up the discharge of impulses from whatever ganglion cells they make synaptic contact with in regeneration. That is, after regeneration, a long synaptic delay may not be a true indication of a slow fiber making contact with a slow cell.

In the 70-day cat the regenerating fibers could be seen entering the ganglion after a very tortuous course through connective tissue. The majority of the fibers were unmyelinated and ran in groups of 5 to 10. Fibers branched into fine fibrils which made contact with ganglion cells and their dendrites by means of boutons de passage and boutons terminaux (Fig. 6).

Electrical studies showed an increase in the speed of conduction in the regenerated preganglionic fibers. The records indicated an intermediate stage between the incomplete regeneration in the 44-day cat and the full regeneration in the 92-day cat. The ganglion of the 92-day cat showed the restoration of the fine intercellular plexus. Many of the thinnest fibrils could be traced to the surface of ganglion cells where boutons de passage not more than 1μ in diameter could be seen. Most fibers were as yet unmyelinated. Figure 7 shows both a bouton terminal and a bouton de passage on a large ganglion cell.

The conduction rates in the regenerated preganglionic fibers ranged up to 7 m. per sec. for the S_1 fibers and to about 2 m. per sec. for the S_2 fibers (these are from $\frac{1}{3}$ to $\frac{1}{5}$ of the normal values). The threshold of the fibers was less than in the 44-day and 70-day cats, but was still about twice the normal value. The synaptic delays were 3 msec. for the S_1 fibres and 6 msec. for the

S_2 fibers, approximately normal values (cf. Therman, Forbes and Galambos, 1940). The ganglion cells showed normal inhibition and facilitation responses (cf. Eccles, 1935b). Again there was good evidence that the high-threshold fibers had made contact with the ganglion cells with the longest synaptic delays, and the low-threshold fibers with the ganglion cells with the shortest synaptic delays. There were probably some exceptional fibers, however, since a weak stimulus applied to the preganglionic trunk produced both the large spike potential and a small late negative wave, which might have been due to S_2 cells discharging. A strong stimulus brought out S_1 and S_2 spikes very clearly. (Fig. 10 e,f).

Discussion

The normal action potentials recorded after antidromic stimulation in cases where all preganglionic fibers had degenerated, confirms the histological evidence that sympathetic ganglion cells are not affected by the loss, through degeneration, of the synaptic endings of preganglionic fibers. Also, the ganglion cells show the normal responses of facilitation and inhibition as soon as the regenerating fibers make contact with them. The synaptic delay of the ganglion cells is the same at the beginning of regeneration as it was before degeneration, showing that the regenerated synapses, from the start, closely resemble normal synapses.

Degeneration in the sympathetic nervous system has been shown to follow the course of that in the central nervous system (cf. Hoff, 1932, and Gibson, 1937), but it is somewhat slower.

A certain amount of histological confirmation of the division of the ganglion cells into S_1, S_2, S_3 and S_4 types has been brought by Solovieva (1937) who has described at least three distinct groups, on the basis of the ratio of cell area to nuclear area.

There has been much speculation whether the finest fibrils can transmit impulses to the ganglion cells by a number of non-specialised contacts. On the basis of the present results it might be said that the boutons shown were not numerous enough to be considered the only synaptic structures. However, the staining methods at present available make it impossible to say with any certainty that all the boutons present were stained.* It cannot be too strongly emphasized that no evidence whatever has been found to support the claim of Stöhr and his pupils that there is protoplasmic continuity across sympathetic synapses. Everything observed in this work has been in favor of discontinuity.

Finally, the imperfections of silver staining make it necessary for any investigator to leave room for possible non-specialised contacts as synapses. The history of the discovery of boutons in other parts of the nervous system in numbers sufficient to account for synaptic transmission, suggests that the boutons in the sympathetic nervous system may eventually be shown to be the specific synaptic agents.

* Improved staining techniques are now in process of development by Prados (1939) and Leach (1939), the former using vitamin C as a reducer in the Cajal techniques for blocks, and the latter using a special haematoxylin stain for boutons.

Summary

A series of experiments is recorded in which the progressive stages in the degeneration and regeneration of synapses in the superior cervical sympathetic ganglion were studied histologically by silver stains, and physiologically by the cathode-ray oscillograph. Transmission through the ganglion diminished with the progressive experimental degeneration of the boutons attached to the preganglionic fibers. Restoration of normal function in the ganglion returned when the regenerating preganglionic fibers re-established contact with the ganglion cells by means of boutons de passage and boutons terminaux. Evidence is presented which strongly suggests selective regeneration of S_1 fibers to S_1 cells, etc. No histological or electrical evidence was found which would indicate that the ganglion cells suffered in any way from the degeneration of the synaptic contacts on their surface. The experimental results confirm unequivocally the theory of structural discontinuity in the sympathetic nervous system.

The research here reported was carried out in the University Laboratory of Physiology, Oxford, and in the late Instituto del Cancer, and the Laboratorio de Histología Normal y Patológica in Madrid. The Osler Trustees and the Christopher Welch Trustees of Oxford University made generous grants for study in Spain under Dr. Pio del Rio-Hortega and for visiting the laboratories of Prof. De Castro, Prof. Stöhr, Prof. Boeke, and Prof. Lawrentjew. Dr. J. C. Eccles carried out the electrophysiological recordings and supervised the work. Prof. Lawrentjew has kindly permitted the reproduction of Fig. 8. Professor Wilder Penfield generously extended the use of the photographic facilities of the Montreal Neurological Institute for the preparation of the illustrations.

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STUDIES OF MOTOR PERFORMANCE AFTER PARIETAL ABLATIONS IN MONKEYS*

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INTRODUCTION

IN MAN and even in the inarticulate monkey, *motor* paralysis may be to some extent differentiated from paralysis of *sensation*, but it is difficult in either form completely to distinguish the purely motor symptoms from the changes in motor performance which result from interruption of the afferent portion of the reflex arc. Thus a limb may for a time hang motionless and flaccid when either an afferent or an efferent spinal root is severed, and it is only through detailed analyses of the syndrome that one may differentiate the underlying causes. The effects on motor performance of cortical ablation involving more complex sensory levels of integration are more difficult to analyze since the parietal cortex contains motor Betz cells (Betz 2, Levin, and Bradford 10); furthermore, the motor areas receive direct thalamo-cortical projections (Polyak 11); and hence the cortical motor and sensory areas cannot be anatomically separated. Physiologically the sensorimotor cortex has been described as a unit by Dusser de Barenne (4).

The sensory defects which follow lesions of the parietal cortex have been described in man (Head 8) and monkeys (Ruch 12), and are known to be due to changes in both the tactile and proprioceptive elements of sensation. Alterations in motor performance also appear, and such "ataxia" has been described in man by Head (8), Guthrie (7), and others. In the present paper an attempt has been made to study the alterations in *motor* performance which ensue in the monkey after pure parietal lesions and to compare them with those which follow lesions of areas 4 and 6 of the precentral cortex.

METHOD

In 11 monkeys (8 *M. mulatta* and 3 mangabeys [2 *Cercocebus torquatus atys* and 1 *C. galeritus chrysogaster*]) unilateral and bilateral ablations were carried out involving part or all of the parietal lobes. In one animal the depths of the central sulcus were incised to sever transcortical U-fibers; in two others complete deafferentiation of a single extremity was followed by a contralateral postcentral cortical ablation. General behavior, neurological status and particularly motor hand performance were studied before and after operation.

OBSERVATIONS

The principal observations are covered in the following illustrative protocols:

EXPERIMENT 1. *Seriatim ablation of left areas 3-1-2; right areas 3-1-2; left areas 5 and 7; right areas 5 and 7. Transient dysmetria, ataxia; permanent hypotonia and marked bilateral atrophy, knee jerks hyperactive. Placing and hopping responses abolished* [P.C. I].

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This animal was a normal immature sooty mangabey male weighing 1.8 kg. Hand performance previous to operation was described as follows: "Either hand is stretched forward for small bits of food. Fingers reach somewhat beyond and as soon as the palmar aspect of the fingers touches the food they are flexed and the food scraped toward the palm where it is held. If the particle is solid like a fragment of peanut, the thumb is put into play with a partial opponens function against the action of the middle and index fingers."

First operation—Left postcentral gyrus (Apr. 22, 1938): The left postcentral gyrus (areas 3-1-2; Fig. 1) was removed, dissecting out all tissue to the depth of the central sulcus. On the following day there was no definite paresis on the right side. "The right hand and foot were held more in extension than the left. They appeared limp and showed no trace of the associated movements of the normal limbs. Walking and climbing were performed well with some overreaching of the right extremities. Food was approached with the left hand and brought to the mouth. Then the right hand was also placed on the food and thus assisted in feeding."

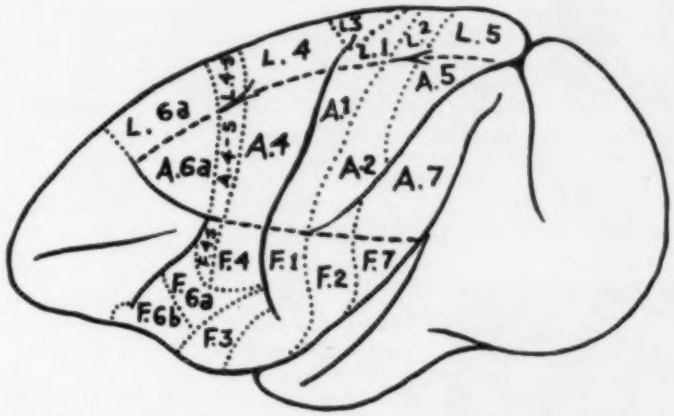

FIG. 1. Map of areas of monkey's sensory cortex (*Macaca mulatta*) (After Dusser de Barenne, J. G., McCulloch, W. S., and Ogawa, T. *J. Neurophysiol.*, 1938, *1:* 436–441).

During the next two weeks the left hand was always used in preference to the right. When the right was used it appeared weaker and although able to grasp and pick up small objects, had less clearly defined movements of the fingers. Locomotion and ordinary cage activity appeared normal except for occasional exaggeration of movements of the right arm and leg in stepping. Resistance to passive manipulation in the right extremities was diminished and the knee jerk was pendulous. There was no atrophy. Placing and hopping reactions were absent in the right lower extremity.

Second operation—Right postcentral gyrus (May 18, 1938): The right postcentral gyrus was removed (areas 3-1-2). Again care was taken to extirpate to the depth of the central sulcus. One day after operation the animal fed itself using both hands, the right hand now showed greater dexterity than the left and, probably because it was now the more skilful of the two, it was used more and better than before the second operation. "In walking and climbing the left extremities hand and foot were everted slightly. Movements were quick and surprisingly accurate. In picking up food there was slight hesitation and the animal would look at the food for 2 or 3 seconds before initiating movement." There was a tendency to hold the left arm and leg extended. They appeared flaccid and sometimes dragged behind in walking.

One week later both hands were used thus: "For small bits of food the thumb is dextrously adducted against the side of the index finger. The monkey inverts its hand and then using mainly lips, tongue and teeth manages to get the food into its mouth." A wild grab was the most usual method of procuring food and there was never a true use of the opponens function, *i.e.* apposition of thumb pad to index or middle finger pads. A week later (May 31) posture was normal except for slight eversion of the hands and feet. "The animal

jumped, climbed and grasped showing no difficulty. When offered peanuts it reached through the bars picking them up and shelled them using both hands." Knee jerks were hyperactive.

Third operation—Left posterior parietal region (July 7, 1938): The remaining portions of the left parietal lobe (areas 5 and 7) were then ablated. Following this there was an additional deficit in motor performance, chiefly a tendency to exaggerate movements in walking and climbing. Often the right extremity became "lost" or tangled in the bars or chain. Resistance to passive manipulation was slight on either side but less on the right than on the left. Placing and hopping were bilaterally absent. The animal fatigued easily and atrophy of thigh muscles began to be noticed. From this time until the fourth operation the right fingers were used less than the left. On both sides vision was used noticeably in guiding the fingers. Food was grabbed and not deftly picked up. It was often dropped. The right hand was more affected than the left. Later although placing and hopping reactions were absent on the right, hopping and proprioceptive placing could be produced with strong stimuli on the left.

Fourth operation—Right posterior parietal lobule (Nov. 16, 1938): On the day after removal of the right areas 5 and 7 resistance to passive manipulation was equally reduced on both sides. Knee jerks were active and pendulous. Placing and hopping responses were absent bilaterally. Cage behavior was cautious and the animal remained on the floor supported on a broad base. Sensory deficit was very evident and in attempting to pick up food it groped and pulled at its own toes until it saw what was happening. The right hand was used in preference for feeding. No precise finger movements were seen. There was a fine tremor. Often the fingers became twisted with each other and at times the hand could not be extended through the wires of the cage without getting caught in various ways. This was true of either hand but the left was less accurate than the right.

By December 14 extreme wasting of all muscle groups in all extremities was noted. Knee jerks became increasingly active while hypotonia persisted. During the next 6 months there was little improvement. Ordinary cage activity was performed normally with only a slight eversion of the hands and feet. Fingers and toes were extremely plastic, atrophy was very great and fatigue easily induced. Loss of postural sense was obvious as bizarre postures and accidental striking and hitting against objects occurred constantly. Placing and hopping reactions remained absent, fine finger movements were grossly awkward.

FIG. 2. Fine prehensile finger movements of "grooming" in a mangabey (Exp. 2) following bilateral removal of parietal lobes.

EXPERIMENT 2. *Seriatum ablation of left areas 3-1-2; right areas 3-1-2; left areas 5 and 7; right areas 5 and 7. Contralateral transient hypotonia. Eversion of hands and feet, permanent awkwardness in grooming; abolition of placing and hopping responses* [P.C. II].

The subject, a mature female "brown mangabey" (*Cercocebus galeritus chrysogaster*) was particularly fitted for observation as it was tame and fond of "grooming," a procedure in which fine movements of fingers and thumbs are necessary (Fig. 2). "The picking finger, always the index, is kept almost straight and the others are semiflexed. When a scale is loosened it is picked up between thumb and first finger. A hair is also held in similar fashion between thumb pad and index pad."

First operation—Left postcentral gyrus (May 26, 1938): The left postcentral gyrus was removed (areas 3-1-2), care being taken not to injure the rostral lip of the central sulcus. One day later the animal would pick up objects with the right hand but although power was good it tended to use the fingers either too strenuously or too softly. It used its

mouth often rather than attempt thumb and finger in apposition. Slight hypotonia especially of the fingers was noticed. Three weeks later use of the right fingers was still awkward. That of the left continued accurate. No other deviations from the normal were noticed.

Second operation—Right postcentral gyrus (June 15, 1938): The right areas 3-1-2 were then extirpated, following which it was noted that the left extremities hung limp and that tactile placing was bilaterally absent. In picking with the left index finger, the animal used random full movements of the arm instead of discrete movements at the phalangeal joint. The amount of pressure was not controlled and often in grooming the fingers bit too deeply. Attempts to put either hand between the bars of the cage were defeated many times by inability to hit the opening. Posture, both while static and in motion, was. normal.

During the next four months there was some recovery of precision in grooming. Resistance to passive manipulation became normal.

Third operation—Left posterior parietal lobule (Nov. 23, 1938): The left areas 5 and 7 were then removed. Immediately an added deficit appeared in the fingers of the right hand although in all other cage performance there was no change noticed. "In grooming it usually reaches for my arm with its left hand and holds it very accurately. It then begins to move the right hand in an attempt to groom but either catches its fingers on the bars of the cage or scratches them along my arm. Very soon it becomes disgusted and then uses the left hand in accurate grooming movements."

Fourth operation—Right posterior parietal region (Dec. 16, 1938): The remaining posterior parietal region (areas 5 and 7) was then removed from the right hemisphere. During the first day after operation no attempt was made to groom with either hand. During succeeding weeks, however, it resumed this occupation (Fig. 2). In April, 1939 posture was normal except for slight eversion of the hands and feet. Placing and hopping responses were bilaterally absent. In grooming all fingers were used instead of the thumb and index finger only; fine prehension was absent and the intensity of pressure of the fingers was very variable and not well controlled. The deep reflexes were active; resistance to passive manipulation seemed normal.

EXPERIMENT 3. *Ablation of left areas 1–2, 5, 7. Right transient hypotonia, weakness and propioceptive loss, permanent tactile loss. Ablation of right posterior parietal area: Transient left hypotonia and depression of knee jerk; fine finger movements poorly done; ultimate deficit greater on right than left* [P.C. VI].

First operation: The left parietal lobe (1–2, 5 and 7) was removed from a rhesus monkey (Oct. 12, 1938) with the exception of area 3, the posterior lip of the central sulcus, which was left untouched so as to be certain that no precentral tissue was inadvertently damaged. The animal then showed transient depression of the knee jerks and limp extremities together with preference for using the normal hand in all fine manipulations. Placing and hopping reactions were at first absent, later hopping returned.

Second operation—Right areas 5 and 7 (Dec. 2, 1938): The right posterior parietal region only was then removed. The right hand immediately thereafter became used temporarily in preference. Tactile placing was absent on both sides, hopping absent on the left.

On the 8th day the use of fingers was still too coarse to permit feeding with small objects unless vision was used to correct movement. Resistance to passive manipulation was less in the left leg than in the right. Eventually, the greater deficit in all these motor acts appeared on the right extremity opposite the larger lesion. Hypotonus was greatest on the right. The left hand was used in preference and its manipulations were better than were those of the right hand. The normal smoothness of prehension was absent being replaced by jerkiness and occasional tremor. But the fingers of the left hand by January 1, 1939 were able to pick up objects by apposition of thumb and index finger. Hopping responses then became bilaterally present. Tactile placing returned on the left but not on the right.

EXPERIMENT 4. *Section of transcortical fibers between left areas 4 and 3; transient hemiparesis. Recovery. Ablation of left parietal lobe: Reappearance of slight deficit in right extremities, especially fingers* [P.C. V].

First operation—Section of left U-fibers (June 14, 1938): Fibers in the depth of the central sulcus were sectioned through its length thus dividing connecting fibers between

areas 3 and 4. A transient hemiparesis resulted characteristic of area 4 ablations. Knee jerks on the right became pendulous, placing and hopping responses disappeared but later returned. Recovery of motor function also appeared complete before the second operation.

Second operation—Left parietal lobe (Dec. 9, 1938): After removal of the left parietal lobe in its entirety there followed immediately a postural defect characterized by pendulous dangling of the right arm and leg during locomotion. Placing and hopping responses disappeared on the right and remained permanently absent. Resistance to passive manipulation did not seem diminished but the right knee jerk became more pendulous and the right extremity showed eventually slight atrophy.

The fingers of the right hand were never used by preference for those of the left. All movements of the right fingers were, however, quickly accomplished and there was very little deficit save in the finest digital movements. Inaccuracy in gauging distance and strength could then be observed.

From the above observations and those made on 7 additional animals, it is evident that the motor deficit which follows parietal lesions is specific and can be clearly distinguished from the syndromes which follow ablation of area 4 or 6. Unilateral removal of areas 3-1-2 or of 1-2 alone caused identical changes, and removal of areas 5 and 7, changes which were similar in quality, but less in duration and intensity. Unilateral ablation of all of areas 3-1-2, 5 and 7, or *bilateral* ablations intensified all symptoms which appeared after the less extensive lesions. In bilateral preparations when the tissue removed from one parietal lobe was greater than that from the other the deficit was greater in the limbs opposite the *larger* ablation.

Fine motor acts were most noticeably affected. The normal hand or foot was always used in preference to the paretic. When the affected digits were used for fine prehension, lack of precision in direction and extent of individual movements was obvious particularly in grooming which requires highly delicate coördination. Accuracy was increased when the animal focussed visual attention on the act. The grosser movements about the cage showed the same type of deficit; the affected extremities assumed bizarre postures and became tangled in perch or bars.

Effect of emotion.—In contrast to changes seen following ablation of either areas 6 or 4, emotion of any sort in the animal with parietal ablation made movement of the paretic limb more sure and accurate. Thus an animal sitting motionless in a cage would show unusual posture until the sight of food or a rage paroxysm sent it into action. Under these stimuli the affected extremities were moved appropriately and gross movements were carried out almost perfectly.

Postural changes.—Immediately after partial or total parietal ablation the contralateral limbs were limp and dangled usually in more extended posture than was normal. Some eversion of hands and feet, and abduction of the extremities was often present. They appeared paralyzed until during some movement one saw perfect flexion, extension, etc. at all joints. At this stage the extremities, if used, appeared weak and tended to "give" beneath the weight of the animal. With improvement in motor function there was diminution in the limpness and a gradual return to bilaterally similar posture. Often sensory loss was demonstrated by the assumption of awkward

positions, a leg might hang through a bar, the fingers of the hand might be doubled under. Attention by the animal or movement often corrected this fault.

Placing and hopping reactions (Bard 1) disappeared immediately following partial or complete parietal ablations in our series of animals. In *partial* lesions, either unilateral or bilateral, hopping and *proprioceptive* placing returned but *tactile* placing continued absent. In partial lesions of the post-central gyrus which excluded area 3, hopping reactions returned, but if area 3 was included in the ablation neither placing nor hopping responses returned during the period of observation. If the entire region, areas 3-1-2, 5 and 7, was extirpated all forms of placing and hopping responses were permanently abolished. With unilateral lesions, crossed placing (*i.e.*, response of paretic extremities to stimuli applied to normal side), could be demonstrated, indicating a sensory, but not a motor defect in this reflex.

The normal response to bringing an object such as the examiner's finger against the sole of a monkey's foot is a quick, apparently involuntary, grasp of that object. This disappears following removal of area 4 and does not return, although the general behavior of the extremities may in every other way approach the normal. This grasp must be in response to tactile stimuli because it appears after the slightest contact with the sole. It is absent after total ablation of areas 3-1-2, 5 and 7. It is present, however, in animals which, following ablation of 3-1-2, or 1-2 have reacquired hopping and proprioceptive placing, but in which tactile placing has remained absent, thus indicating two forms of response to tactile stimuli integrated either in different regions in the parietal cortex or to a different degree, so that one may at times be present, the other absent.

Tendon reflexes.—Immediately after operation tendon reflexes, as shown by biceps and knee jerks were always diminished. The term *pendulous* characterizes the response. At the same time diminished resistance to passive manipulation appeared and continued for some weeks. Eventually resistance again approximated that of the normal side and the knee jerks then were more active, but hypotonia of mild degree remained throughout the duration of the experiments. No abnormal reflexes, *i.e.*, no Babinski, Rossolimo or Hoffmann responses ever appeared. There was never an increase of resistance to passive manipulation, but diminished resistance was present after all ablations.

Atrophy of muscles followed extensive parietal ablations in one instance (Exp. 1), but was not noted in another similar ablation (Exp. 2). The subject of atrophy is one requiring further study.

Bilateral ablations, either partial or complete, merely increased the intensity of all symptoms. Apparently there was permanent loss, both tactile and proprioceptive, if all of areas 3-1-2, 5 and 7 were removed, as all placing and hopping responses were absent in two mangabeys (Expt. 1 and 2) six months after such ablations. These animals then showed noticeable awkwardness in prehension and diminished resistance to passive manipulation.

In another animal six months after bilateral removal of areas 1 and 2, tactile placing was still absent, although proprioceptive placing and hopping had returned. This animal showed no defect in posture or in gait, but fingers were used less well than is normal (P.C. 7).

Deafferentation.—Following deafferentation of a limb a monkey recovers some motor function. It was thought that if this recovery was sufficient a secondary parietal ablation might then alter motor performance. If this occurred it would indicate interruption of motor efferents from the parietal lobe. In the two animals used, however, the recovery following deafferentiation was slight and *secondary parietal ablation produced no change in motor behavior whatsoever.*

Effects of ablations of areas 4 and 6.—For purposes of comparison, a brief outline is here included of the motor syndromes which follow ablation of the precentral motor areas (Fulton, 6), as observed in this laboratory in another series of monkeys.

Removal of area 4, the motor area, produces in the monkey immediate "volitional" paralysis of all the muscles of the extremities, most marked distally and least proximally. Tendon reflexes are depressed or abolished as are placing and hopping responses. There is flaccidity at all joints followed in the third week by transient spasticity of the digits (Denny-Brown and Botterell, unpublished). The impairment of fine movements of the digits is permanent. All movements are noticeably less well coördinated when under excitement, rage or any other emotion.

Areas 6 and 4-s. The most obvious effect of removal of area 4-s, the "strip" region of Hines (9) lying between areas 4 and 6, is transient spasticity of the extremity with loss of the finer movements of the digits. The increase in resistance to passive manipulation becomes gradually less, but fine digital prehension is never reacquired. Ablation of area 6 causes reflex grasping with some temporary increase in resistance to passive manipulation and impairment of skilled movements; recovery following unilateral ablation of area 6 is nearly complete.

Discussion

The motor deficits which follow any cortical ablations are thus alike in that they affect most severely the distal portions of the extremities, in particular fine movements of the fingers; and that, in every instance, tendon jerks and resistance to passive manipulation are altered temporarily. But the motor syndrome which follows precentral lesions may be clearly distinguished from that of a postcentral purely by observation of behavior. Analysis of each syndrome brings out the following differences: (i) A true motor paresis follows ablation of either area 4 or 6; movement is inaccurate and there is inability to perform fine movements; (ii) attempted finger movements are slow and remain without individual components even after maximum recovery has occurred. Following parietal ablations fine movements are also inaccurate, but this is corrected by close visual attention; all movements are quick, and the fingers are capable of individual discrete movements although they are poorly adjusted in range and direction. (iii) A noticeable loss of tactile and position sense always accompanies the motor deficit of a parietal lesion. (iv) Emotional disturbances render fine movements less well performed after any motor area extirpation, but better performed after any postcentral lesion. Thus, following a lesion of the motor

cortex either in a spastic or flaccid state emotion always makes motor activity less controlled than if the same act is carried out under quiet conditions without excitement. A spastic limb in particular becomes uncontrollable, forced grasping will become more extreme and all the associated and involuntary movements are brought into play, making voluntary and purposeful accomplishment impossible. These associated movements never appear with parietal lesions.

As in Bard's series of postcentral ablations tactile placing in our animals was more greatly affected by parietal lesions than was either hopping or proprioceptive placing. The placing reaction to tactile stimuli was permanently abolished in all ablations of the postcentral gyrus or of the entire parietal lobe. In one instance, following ablation of areas 5 and 7 only, tactile placing returned after a short absence but the threshold was then higher than before operation. In every case of parietal ablation proprioceptive responses were also altered, but to less degree if the ablated area was incomplete. Immediately following removal of areas 3-1-2, or 5 and 7, these proprioceptive responses were absent. Shortly they reappeared but were less brisk and required greater stimuli. Later they returned to nearly normal level. They were less affected by ablations of areas 5 and 7 than of 3-1-2 or, of 1-2. Following bilateral removal of areas 1-2, 5 and 7 in one instance and of areas 3-1-2, 5 and 7 in another, hopping and proprioceptive placing, as well as tactile placing, were permanently lost.

These findings are in agreement with those of Bard that cortical parietal regions have less influence on the normal response of proprioceptive placing than of tactile placing. Proprioception must, however, be represented cortically in postcentral regions since slight though permanent alteration in response may appear after small parietal lesions and since proprioception is permanently affected (as demonstrated by hopping and placing) if all the parietal lobe is removed from both hemispheres.

The "hypotonus" or decrease in resistance to passive manipulation which was present to some degree in all operated extremities may be also accounted for by proprioceptive loss. If the normal status at a joint either resting or moving is maintained by the reflex lengthening and shortening reactions of muscles connected with that joint then alteration in the status of the stretch reflex will alter the total response of that joint. As the stretch reflex is reduced so resistance to passive manipulation will be less. In the extreme of tabes a flaccid joint results and the "hypotonus" of the parietal syndrome may well be due to disturbance of the same mechanism. Following parietal lesions, however, knee jerks were only temporarily diminished, and later in some case appeared to be increased, so that serious permanent impairment of this reflex arc cannot have occurred.

In one animal the arcuate fibers at the depth of the left central sulcus were cut at a first operation. Transient, true motor paresis followed, perhaps due to pressure on the Betz cell area at the time of operation. Following complete recovery from this, six months later, the left parietal lobe was

excised. Alterations in motor performance following this were of the degree and type seen after primary ablation of this area. The effect on motor performance of such a parietal ablation cannot then be due to a direct effect on motor cortex. The same effects have been observed when a postcentral lesion is made after recovery from complete ablation of area 4.

Localization within the parietal lobe.—In this series there was some indication of functional localization within the parietal lobe, but most evidence pointed to a general and non-specific type of functional activity. Lesions of the postcentral gyrus (areas 3-1-2) caused temporary changes in motor performance, and in response to proprioceptive stimuli. Tactile placing response was permanently lost. Partial lesions of the postcentral gyrus (areas 1-2) were also made leaving areas 3, the posterior lip of the postcentral sulcus, untouched. This was done to be certain that no inadvertent damage to motor area 4 had occurred. The effects on motor performance were similar to those following ablation of areas 3-1-2, except that in the smaller lesion tactile placing was only temporarily impaired.

Bilaterality of function is much less noticeable in the parietal than in the frontal lobe. Ablation, either at a first or at a second operation, was followed by little if any effect upon the ipsilateral extremities; also contralateral changes were more enduring and exhibited less recovery once the initial reorganization had taken place, than did motor functions following precentral lesions.

Summary

1. The alterations in motor performance which follow ablations of the parietal lobe have been compared with those due to ablation of areas 4 or 6. Unilateral removal of any of these three areas produces motor disability which in each instance is characterized by relative disuse of the operated, as compared with the normal extremity, and by the greater involvement of distal joints and movements, as compared to proximal. The motor syndrome produced by ablation of any one of these areas may, however, be clearly distinguished from that produced by either of the other two (see Discussion).

2. As demonstrated by placing and hopping responses, tactile deficit appears following unilateral or partial ablation of either areas 3-1-2, 1-2 or 5 and 7. Proprioception is much less affected by these parietal lesions, but complete bilateral removal of all parietal tissue permanently abolishes the hopping and the tactile and proprioceptive placing reactions.

3. Absent or diminished knee jerks, together with diminished resistance to passive manipulation appear immediately after all parietal ablations. Later knee jerks may become hyperactive, but resistance to passive manipulation never becomes increased.

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SOMATIC AND AUTONOMIC REFLEXES IN SPINAL MONKEYS*

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INTRODUCTION

IT HAS LONG been known that somatic reflexes tend, after spinal transection in primate forms, to be depressed completely for some hours, days or even for weeks; eventually they return, however, and certain reflexes may even become hyperactive. Autonomic reactions, *e.g.*, sweating, vasoconstriction and piloerection, also appear in spinal man. No studies, however, appear to have been made of the time of appearance of these autonomic reflexes in relation to the return of somatic responses in primate forms. Since observations of this character are essential for the elucidation of the theory of levels of autonomic function, the following study was undertaken.

HISTORICAL

Nasse (1839) observed that the temperature of the hind legs of an animal with a severed dorsal cord will rise once more when one destroys the isolated distal portion of the spinal cord. Goltz and Freusberg (1874) noted after destruction of the spinal cord in the dog that the vessels of the lower extremities ultimately recovered their habitual tonus. Similar conclusions were reached by Gergens and Werber (1876) on the frog. Further observations along these lines were contributed by Goltz and Ewald (1896). They felt that the lower portion of the spinal cord was unnecessary for the maintenance of the vascular tone of the hind part of the body, and that vascular tone depended upon local adjustments which could be maintained independently. Sugar and Gerard (1940) sectioned the thoracic spinal cords of rats and found flexion reflexes immediately after the operation, crossed reflexes after 3 days, and scratch reflexes after 11 days. The bladder became automatic in 7 to 10 days. In some of their rats following a month of characteristic spinal reactivity, further sensory and motor recovery began slowly to occur, and the investigators were led to conclude in these instances that true anatomical and physiological *regeneration* had occurred. Thauer (1935) demonstrated that the rabbit was able to maintain its body temperature in a fairly efficient manner after a period of time following cervical cord section. Popoff (1934) described recovery of temperature regulation following destruction of the spinal cord and cervical section of the vagi in the dog. He concluded that this regulation was made possible by peripheral plexuses and ganglia. Hermann, Morin, and Cier (1937) studied the local effects of cooling the paw of the dog before and after section of the sciatic nerve. The denervated paw was slightly warmer than its homologue during the first 2 or 3 weeks following the section. The denervated limb, however, cooled to the same degree as the one with intact innervation (18–20°C.). These authors (1938) emphasized that recovery of vascular tonus took place approximately 4 weeks after destruction of the distal portion of the spinal cord, but they noted that the degree of local cooling was now somewhat less than before ablation of the cord. After cutting the sciatic nerve on such an animal, and allowing 2–3 weeks for degeneration, they observed that the temperature of the denervated extremity now fell in excess of 20°C. after immersion in the refrigerant mixture. Issekutz, Jr. (1937) reported a recovery of ability to maintain normal body temperature in the dog under ordinary room conditions. The same findings were reported in the

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cat by Issekutz, Leinzinger, and Issekutz, Jr. (1937). These results, however, were not confirmed by observations of Sherrington (1924), Freund (1922), or Clark (1940). The experiments of Bowen, Coombs, and Pike (1922) on cats indicated the functional dependence of the peripheral ganglia of the sympathetic system upon the central system.

Cannon (1930) has been able to show that cats, dogs, and monkeys deprived of their ganglionated trunks from stellate to sacral ganglia on both sides continue to live without apparent difficulty in the sheltered surroundings of the laboratory. Zuckerman and Ruch (1934) reported that the changes in plantar temperatures of macaques which normally followed abrupt fall or rise in environmental temperature, were slower and much less marked after the effects of spinal shock had worn off.

The observations of Head and Riddoch (1917) and Riddoch (1917) on war injuries brought to light many interesting facts concerning immediate and late results of spinal cord injury in man. The immediate effects of complete transection were absence of all reflexes below the lesion, paralysis of the rectum and bladder, and total loss of activity of the sweat glands. Later the reflexes returned and became exaggerated, the rectum and bladder began to function regularly, and the skin became soft and moist. Leriche and Fontaine (1927) reported that low thoracic section of the cord leaves normal vasomotor reactions in man unchanged. They found after extensive destruction of the cord (D8-D10), that all vasomotor reactions persisted in the lower limbs at the end of three months. They concluded that these effects were due to the existence of extramedullary vasomotor centers which one finds partly in the sympathetic nervous system, and partly in the walls of the vessels themselves.

Studies on somatic reflexes after spinal section have been carried out by a number of observers, including Sherrington (1899), Fulton and Sherrington (1932), Fulton and Keller (1932), Fulton and McCouch (1937), and Hinsey and Markee (1938). The return of knee jerk and ankle jerk reflexes, toe signs, withdrawal reflexes, and the like, have been intensively followed and recorded. A number of investigators, including Cooper and Sherrington (1933), Fulton and McCouch (1937), and Hinsey and Markee (1938) have noted the appearance of areflexia in the late stages of spinal section and in monkeys have established the connection between this condition and degeneration of the sciatic nerves (owing to pressure).

Brown-Séquard (1852) credited Edwards with the observation that chilling of a single part of the body, such as the hand or foot, caused a fall in temperature of the other parts of the body without inducing measurable changes in body temperature. Brown-Séquard expressed the opinion that cooling of an immersed part in very cold water produced painful stimuli which, in turn, excited nervous influences resulting in a fall of temperature of non-immersed portions of the body. Stewart (1911) measured such changes calorimetrically in man. We came to the conclusion that this same immersion test could be applied to monkeys as a convenient means of observing the rate and amount of return of vasomotor function in these animals after spinal transection.

METHODS

Female monkeys (*Macaca mulatta*) were used, their skin temperature being recorded by means of a Leeds-Northrup machine (Micromax), which gave continuous recordings of temperature. The monkey was placed in a holding box without anesthesia. It was restrained in a symmetrical position with both feet free, care being taken that the circulation to the lower extremities was not embarrassed. Waterproofed leads were applied to the palmar surface of the web between the hallux and the first toe on each extremity, and were held in place by a strip of adhesive tape applied loosely around the foot. Simultaneous recordings were made from a lead inserted in the rectum. The experiments were conducted in a small closed room which could be maintained free of drafts at a temperature of 78°F. After a control period, one lower extremity, generally the right, was immersed to the mid-calf in a quart jar containing broken ice cubes, and kept immersed for 20 minutes. The lower extremity, incidentally, was used as a stirring rod to keep the ice water moderately agitated. Care was taken to insulate the jar containing ice-water so that the non-immersed extremity would not come in contact with it. Temperatures of the immersed, as well as the non-immersed portions of the body were thus recorded automatically by the Leeds-Northrup instrument. After several control observations, various operative procedures were carried out on the monkeys and the state of the somatic reflexes, function of the bowels and bladder, piloerection, and the return of the sweat secretion were noted, in ad-

dition to the vasomotor status. The appearance of sweating was observed by smearing a thin layer of vaseline over the sole of the foot and noting the accumulation of droplets of sweat beneath the film. Section of the cord was carried out at various levels, in addition to supplementary procedures, to be mentioned later. The autonomic functions of the animals were studied in some cases immediately after the operation, and in others within a few hours after the operative procedure. As many of the animals were studied from day to day as could be accommodated; in most instances from three to four readings per week were obtained on each animal. The spinal transections produced, in all instances, the well known condition of "shock." Special postoperative attention was paid to care in the attempt to keep the animals alive as long as possible and to avoid pressure on their sciatic nerves. Manual expression of urine from the bladder was carried out until that organ became automatic. The animals were placed on a thick straw bed in their cages; the holding boxes were well padded to avoid pressure on the buttocks. At the conclusion of the series of experiments the animals were sacrificed and at autopsy the level of the operation was identified. The cords were sectioned longitudinally through the site of the operation and stained with hematoxylin and eosin, silver stain for axis cylinders, myelin sheath stain, and toluidin blue stain. The sciatic nerves were removed, in most instances, and stained with osmic acid.

Results of Spinal Transections

Skin temperature readings in the normal animal are illustrated by the first monkey in this series. This animal (No. 1141) was an immature female *Macaca mulatta* monkey weighing 2.3 kg. Control studies showed that the skin temperature of the lower extremities seldom remain at a fixed level, even with the animal at rest in a room with constant temperature. Slow rises and falls are the rule. The variations in temperature are not abrupt, but over the course of an hour the fluctuations may amount to a degree or more, Fahrenheit. The average temperature in the web of the hallux and first toe is approximately 90°F. in a room temperature of 78°F. The usual rectal temperature under these conditions is 101°F. Immersion of the right lower extremity in ice water produces an abrupt drop in temperature in the left, or non-immersed extremity (Fig. 1). The average fall in 4 such observations on this animal was 4°F. in 20 min.

Experiment 1. *Spinal transection in macaque at Th5; 5 months survival; return of crossed cooling on 42nd day. Removal of spinal cord below transection; abolition of crossed vasomotor reflexes; sacrifice 5 days later.* [No. 1141]

First operation: On January 14, 1939, under ether anesthesia, a laminectomy was performed under aseptic conditions and the cord transected at the 5th thoracic level. Examination immediately after the animal had recovered from the effects of the anesthetic revealed completely flaccid lower extremities, all reflexes in the lowers being abolished. There was complete analgesia to pin prick below the fifth dorsal level. The lower extremities were warm and dry, and piloerection was absent. Gradually the somatic reflexes began to make their appearance. A flickering response of the hallux on stimulation of the outer aspect of the sole was obtained 24 hours after the operation. An adductor reflex was present in 48 hours, knee jerk reflex in 96 hours, ankle jerk in 6 days, and flexor withdrawal in 7 days. The reflexes remained very active as long as this animal was kept alive. *Fifty-one* days after the operation vigorous flexor "spasms" made their appearance. These episodes would occur spontaneously, yet could be induced readily by stimulation of the perineum. The legs would draw up, the toes would spread, and the animal would make slow running movements to the accompaniment of vigorous tail wagging. The bladder and bowels became automatic by the end of the 6th day, sweating and piloerection appeared on the 14th day after the operation. At no time, however, were these two latter functions as active as they were before the operation.

Attempts to cool the left foot by immersion of the right in ice-water immediately and

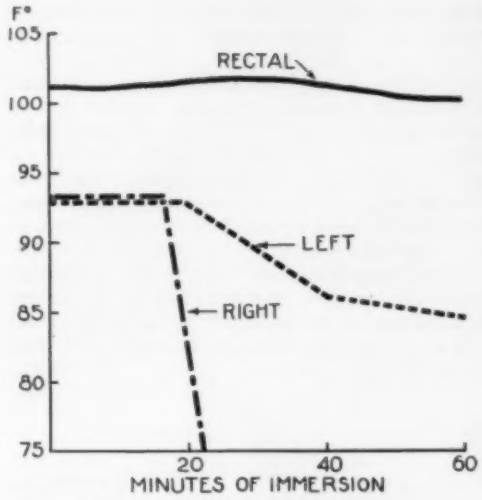

FIG. 1 (Expt. 1). Left (See text).

FIG. 2 (Expt. 2). Right.

for a number of days after the operation were unsuccessful. The skin temperature of the lower extremities was relatively high (Fig. 2). Specifically, the temperature of the lower extremities was 96°F., while the rectal temperature was now 97.5°F. On the 42nd day after operation, a significant indirect cooling response made its appearance, as indicated in Fig. 3. A summary of the rate of appearance of these functions in this, as well as the other animals on which transections of the cord were performed is shown in Table 1.

The leads were now placed so that one was attached to the left foot, one to the right foot, and one to the web between the hallux and index finger of the left upper extremity. The right foot was then immersed in ice water. During this period of immersion the temperature of the left hand dropped 6°F. while the temperature of the left lower extremity was dropped 3°F. After the indirect cooling reflex had thus become well established, a tourniquet was applied to the right thigh, inflated to 100 mm. Hg, and maintained for 15 min. while the right foot and calf were immersed in ice water. The temperature of the

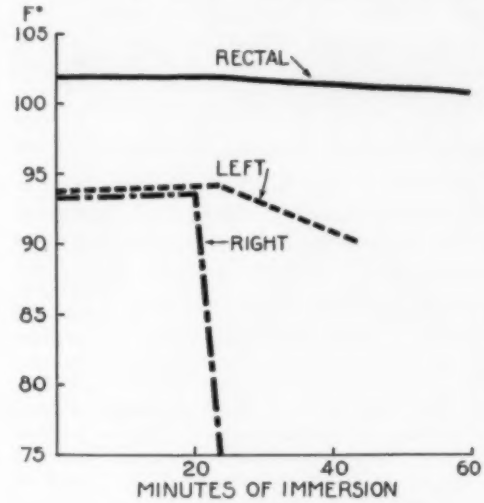

FIG. 3 (Expt. 1). Left (See text).

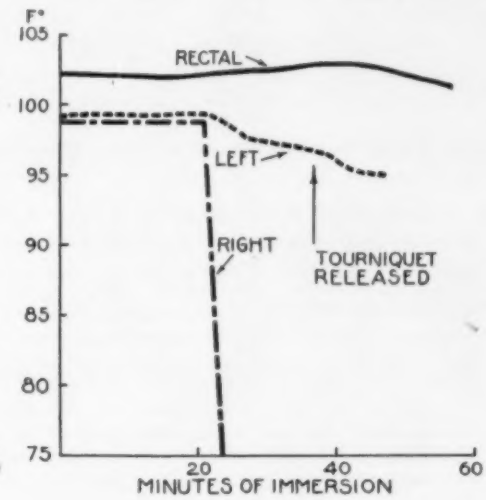

FIG. 4 (Expt. 1). Right.

opposite lower extremity was lowered in spite of the fact that blood was not returning from the immersed extremity. A further fall occurred, however, when the tourniquet was released (Fig. 4).

Second operation—Removal of the distal two-thirds of the spinal cord. On June 23, 1939, under intraperitoneal amytal anesthesia an extensive laminectomy was carried out in order to expose the entire spinal cord below and including the site of the previous operation. It was possible to section the cord one segment above the previous transection and to remove all of the cord distal to that point. Bleeding was controlled with difficulty, but the animal survived the operative procedure. Reflexes, when they were tested 24 hours later, could not be obtained in the completely flaccid lower extremities. The bladder had lost its automaticity and was once more distended. The sensory level was now at D4.

Skin temperature studies showed levels which paralleled and closely approximated the rectal temperature. Once more the indirect cooling response was lost (Fig. 5). However, 0.2 cc. of adrenalin (1–1000) intramuscularly produced a prompt fall in temperature of the left foot after immersion of the right foot in ice-water had failed to do so (Fig. 6). The animal was sacrificed 5 days after the second operative procedure.

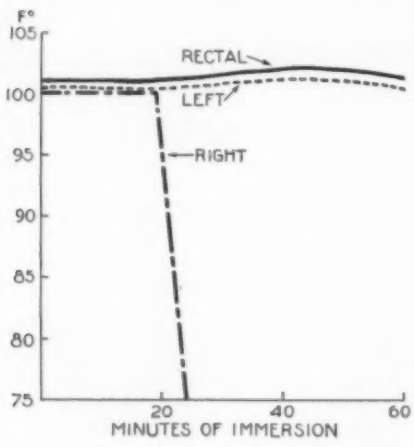

FIG. 5 (Expt. 1). Left (See text).

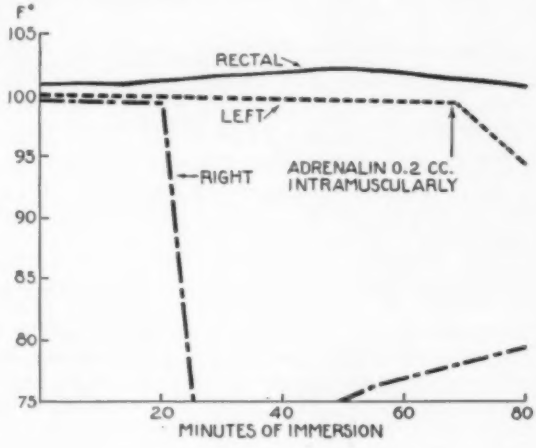

FIG. 6 (Expt. 1). Right.

Microscopic examination of the cord at the site of the first operative procedure showed that the cord section had been complete. The sciatic nerves, removed at the time of autopsy, were found to be intact except for early Marchi degeneration.

Eight other monkeys were used in this series; the results are recorded in Table 1.

The third monkey (No. 1177) in this series showed an average drop of 3°F. in the non-immersed lower extremity before spinal section. As part of the preoperative observations, the effect of a tourniquet applied to the immersed extremity was noted. In the non-immersed foot there was a rather prompt fall of 2°F. in temperature; the curve levelled off, with a further drop when the tourniquet was released.

Spinal transection. Macaque no. 1177. Operation. On February 4, 1939, the spinal cord was transected at the 12th dorsal level. Examination of the animal after it had fully come out of the anesthetic showed loss of sensation below the groins and loss of motor power in the lower extremities, as well as paralysis of the bladder and bowels. A slight degree of piloerection was observed one hour after the operation, and sweating was present during the first day in the lower limbs. The bladder and bowels became automatic by the 3rd day,

Table 1.—Appearance of somatic and autonomic reflexes after spinal transection in monkeys
(Time intervals in days unless otherwise specified)

Monkey No.	1141	1156	1177	1194	1187	1186	1201	1211	1224
Average drop of temperature of non-immersed foot preoperatively (°F.)	4	5	3	3.5	3	3	4	2.5	4
Level of transection	5D	7D	12D	6D	10D	1D	10D	1D	6C
Return of function below level of section (days postoperative)									
Flickering response of hallux	1	1	*	4	4 hr.	2	1	3 hr.	1
Adductor	2	20 min.	*	1 hr.	2	1	1	3 hr.	1
Knee jerk	4	5	*	1 hr.	2	1	1	3 hr.	1
Ankle jerk	6	7	*	1	5	1	1	3 hr.	1
Flexor withdrawal	7	7	*	19	9	22	*	8	*
Automatic bladder	6	5	2	7	5	16	11	11	5
Automatic bowel	6	5	3	3	5	4	8	3	5
Sweating	14	12	1	14	5	22	11	17	*
Piloerection	14	5	1 hr.	4	4	22	11	17	*
Crossed cooling response	42	26	16	52	17	39	*	*	*
Average fall in temperature of non-immersed limb (°F.)	3	3.5	3	3	2	2.5	*	*	*
Sacrifice, or subsequent operation, days after 1st operation	160	145	141	128	100	117	14	19 (pneumonia)	10 (pneumonia)

* Did not appear.

and the indirect cooling response returned on the 16th day. No evidence of return of somatic reflexes was ever found in the lower extremities. It is significant that the indirect cooling response was maintained from the 16th day throughout the remaining period of observation, totalling 141 days after the operation. At time of autopsy and in the subsequent microscopic sections the cord was found to have been severed completely at the 12th dorsal level, and the entire lumbar cord to have been softened and replaced with glial and connective tissue. Specimens of the sciatic nerves stained with osmic acid showed evidence of abundant Marchi degeneration.

The fourth monkey (No. 1194) showed an average preoperative drop of 3.5°F. in the non-immersed lower extremity.

Macaque no. 1194. Spinal transection. On February 18, 1939, a transection of the cord was performed at the 6th thoracic level. Somatic reflexes were well established within the first week. The bladder became automatic on the 7th day, piloerection was observed on the 4th day, sweating on the 14th day, and the indirect cooling response made its appearance on the 52nd day. These reactions were maintained until the animal was sacrificed 128 days after the operation. Shortly before exitus the effect of adrenalin, 0.25 cc. of 1–1000 solution intramuscularly, was tried. A prompt drop of 6°F. in the lower limbs during the ensuing 20 min. occurred. This fall was twice as great as that produced by immersion of the opposite lower extremity of this animal.

Other Lesions—Control Observations

Monkey No. 1196, belonging to species *Cercopithecus mona*, was brought into the laboratory by its owner who stated that the animal had been af-

flicted with progressive paralysis of its lower extremities for 2 weeks. At the time of examination on February 24, 1939, the animal was unable to move its lower limbs, deep reflexes of the lower extremities were hyperactive, and there was hypesthesia below the level of the umbilicus. A drop of 4°F. was found in the non-immersed lower extremity. Autopsy revealed compression myelopathy at the 7th dorsal level as a result of tuberculous granulation tissue in the epidural space.

Monkey No. 1203 proved to have an average preoperative drop in the non-immersed extremity of 4.5°F. The antero-lateral portion of the cord on the left was destroyed by operation at the 5th dorsal level. Five hours after the operation, when the animal was well out of the anesthetic, there was hypotonia of the left leg, which was moved slightly, and pain sensation was reduced on the right lower extremity. Upon cooling the right foot in ice-water 20 min., the temperature of the left fell 2°F. Two days after the operation a drop of 4°F. was obtained; 10 days after the operation there was a drop of 3.5°F. Sixteen days after the first operation the wound was opened, the cord again exposed and a transection made immediately above the previous lesion. The course after the 2nd operation followed that of other spinal transections. The animal went through a period of spinal shock, somatic reflexes began to make their appearance within 24 hours. An appreciable indirect cooling reaction made its appearance on the 27th day after the second procedure, *i.e.*, a drop of 3°F.

Monkey No. 1222 had a preoperative drop in temperature of 5.5°F. in 20 min. in the non-immersed lower extremity. On April 20, 1939, a right lateral semisection was performed at the 9th dorsal level. Examination 4 hours after the operation showed a completely flaccid right lower extremity, with preserved function on the left. Sweating and piloerection were absent on the right and present on the left. Sensibility to painful stimuli was absent on the left lower extremity. The skin temperature of the right foot was 97° and the left 88°F. Immersion of the left foot in ice-water produced a drop of 3°F. in the non-immersed right leg. Sweating and piloerection were much in evidence in the right leg 5 days after the operation, at which time the indirect cooling drop amounted to 5°F. Forty-one days after the operation a drop of 6°F. was obtained. On June 27, 1939, or 68 days after the initial operation, transection of the cord was performed at the 5th dorsal level. After the animal had blown off the ether it was found to have lost all voluntary motion in the lower extremities. The deep reflexes were present and hyperactive on the right but were absent on the left lower. Cooling the left leg in ice water did not produce a drop in temperature in the right, yet there was a drop of 3°F. in the right foot after the injection of 0.2 cc. of adrenalin (1–1000) intramuscularly.

Animal No. 1225 showed preoperative drop in temperature of the non-immersed lower extremity amounting to an average of 5°F. On May 26, 1939, through a transperitoneal approach, a bilateral lumbar ganglionectomy was performed, the ganglia on each side being removed from the level of the

renal vein down to the point where the trunk disappeared behind the common iliac vessels. Three days after the operation the skin of the lower extremities was warm and dry. The temperature of the lower extremities was recorded as 100°F. in each foot, the rectal temperature being 102°F. The indirect cooling reaction could not be produced. This animal was not observed again until June 15, 1939, when the temperature in the non-immersed lower extremity dropped 4.5°F. On June 19, 1939, the femoral and sciatic nerves on the right were sectioned. The animal now had a completely flaccid right leg, the skin temperature of which was *cooler* than the left. Immersion of the right leg in ice-water produced a drop of only 2°F. in the left. Repetition of this same experiment with a tourniquet applied to the right leg so as to occlude the flow of blood from that extremity gave negative results in so far as the temperature of the left leg was concerned. On June 22, 1939, with the animal in the holding box and leads attached to both lower extremities, an intramuscular injection of 0.3 cc. of adrenalin (1–1000) reduced the temperature of the right foot from 91.5 to 87°F. in 20 minutes, and the left from 100 to 96.5°F. in the same period of time. On June 24, 1939, a transection was performed at the 5th dorsal level. On the following day the knee jerk and ankle jerk were present but hypoactive in the left leg. Now the skin temperature of the left lower extremity paralleled and closely approached the rectal temperature but the temperature of the right lower extremity remained from 2 to 4°F. below the figure for the left. Immersion of the right lower extremity in ice-water produced no drop in the temperature of the left which, however, showed an immediate drop upon the injection of adrenalin intramuscularly.

Monkey No. 1179 showed an average preoperative temperature drop amounting to 4°F. in 20 minutes. On May 31, 1939 a bilateral lumbar sympathetic ganglionectomy was performed in a manner similar to that described for Monkey No. 1225. On June 1, 1939, the skin of the lower limbs was warm and dry, in contrast to that of the upper which was cool and moist. The temperature of the skin of each lower extremity was 100°F., the rectal temperature 102°F. Cooling studies on June 2, 1939, showed a negligible drop in temperature of the non-immersed left lower extremity. The next time the animal was examined, on June 16, 1939, the lower extremities, although dry, were much cooler to the touch than they had been immediately after the operation. The indirect cooling response had, by now, returned. On June 20, 1939, the spinal cord was sectioned at the 11th dorsal level. On the following day the skin temperature recordings of the lower extremities were the same as they were prior to the operation on the spinal cord, with indirect cooling of 1.5°F. On June 22, 1939, there was an indirect cooling response of 2°F. When a tourniquet was applied to the right leg, however, the drop was only 1°F. On June 26, 1939, the indirect cooling response amounted to 3°F. The fall in temperature was prompt in both lower extremities after the injection of adrenalin 0.3 cc. intramuscularly.

Conclusions

1. Immersion of one foot of a monkey in ice-water will cause a drop in temperature of 4–5°F. in the opposite lower extremity, as measured by the Micromax recorder. Since this response returns some time after spinal transection, it is unlikely that painful stimuli play the chief rôle in its production. This indirect cooling reaction is present, though less marked, in the normal monkey, if the immersed lower extremity is first constricted with a tourniquet. Release of the tourniquet is followed by a further drop in the skin temperature of the opposite extremity. These observations would indicate that the indirect cooling reaction is mediated both by the nervous system and the blood stream.

2. The term "shock" applies equally to autonomic and to somatic reactions. The immediate effect of transection of the spinal cord of monkeys from the 6th cervical to the 12th thoracic levels is the well recognized state of hyporeflexia, characterized by abolition of all somatic reflexes, paralysis of bowel and bladder function, dryness of the skin, absence of piloerection, and vasomotor paralysis, the latter condition being evidenced by skin temperatures in the feet of a value which parallels and closely approximates the rectal temperature. During this period of "shock" cooling one lower extremity does not cool the opposite limb.

3. The return of somatic reflexes precedes the return of autonomic functions. Certain somatic reflexes may appear within one hour after the spinal transection, and many somatic reflexes become fully established within one week after the operation. Automaticity of the bladder and bowel usually makes its appearance shortly after the somatic spinal reflexes are established. Sweating and piloerection appear usually one week after the bowels and bladder become automatic. Sweating and piloerection, however, are less efficient than before operation. The indirect cooling response, deficient during the period of "shock," makes its appearance after several weeks. In general, the higher the level of the transection, the longer period of time required for this response to return. Upon its establishment following operation, the indirect cooling response is less well developed than before spinal section. Removal of the portion of the cord distal to the original section will once more abolish the indirect cooling response. Injection of adrenalin, however, still causes a prompt fall in temperature in the non-immersed foot when cooling the opposite lower extremity fails to do so.

4. A slowly progressive tuberculous process resulting in a practically complete transverse lesion at the 7th dorsal level led to no significant depression of the crossed cooling response when this reaction was tested two weeks after the onset of the signs of paraplegia.

5. Partial lesions of the cord affect the crossed cooling response much less than complete transection. Lateral semisection of the cord at the 9th dorsal level depresses, but does not abolish this response. Subsequent transection of the cord above the level of the semisection abolishes the crossed

cooling response, in spite of the fact that adrenalin will result in a drop in temperature of the lower extremities.

6. Lumbar (preganglionic) sympathectomy obliterates the crossed cooling response which returns some time within 3 weeks; the stimulus for the response can be elicited through a denervated lower extremity, but not when this denervated extremity has its return blood supply cut off by a tourniquet. Spinal section at the 11th dorsal level now depresses, but does not obliterate the indirect cooling response.

7. Adequate nursing care is imperative in the management of spinal monkeys, and special precautions must be taken to prevent pressure atrophy of the sciatic nerves.

Summary

Spinal cord lesions were made in 14 monkeys. In 9 animals transections were performed at various levels, and observations made relative to the rate and extent of return of somatic and autonomic functions below the level of the lesions. In 3 monkeys the effect of partial lesions of the spinal cord was noted. In 2 such animals observations were made relative to the effect of transverse cord lesions after bilateral lumbar sympathectomy. The term "shock" applies equally well to the autonomic as to the somatic systems following complete lesions of the cord. The return of somatic reflexes precedes the reestablishment of such autonomic functions as piloerection, sweating, and vasoconstriction. Although the autonomic functions return after spinal transection, they do not reach the same degree of efficiency that they exhibit in the normal animal. Cooling of one lower extremity in ice-water normally produces a drop in temperature in the non-immersed lower extremity, but fails to do so during the period of "shock" following spinal transection, or for a short period of time following lumbar (preganglionic) sympathectomy. This indirect cooling response is temporarily depressed after partial lesions of the cord.

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NERVE ACTIVITY ACCOMPANYING FASCICULATION PRODUCED BY PROSTIGMIN

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THE OCCURRENCE of fascicular twitching of muscle following the administration of prostigmin or eserine has been recognized for many years[1,2]. Although it has been thought to result from the action of these drugs on the muscle or the motor end plate, there are certain features of the response which are difficult to explain on this basis.

Thus it is important to observe that the muscle contraction produced by eserine is a grossly visible twitch. It is the movement which results from the simultaneous contraction of a number of muscle fibers. That this group of muscle fibers acts in a synchronized fashion suggests that the contracting fibers may all be members of the same motor unit, and that they are all responding together to a nerve impulse initiated by eserine. In order to examine this possibility, Langley and Kato[3] determined the effect of nerve degeneration on the fasciculation produced by eserine. Section of a nerve causes no immediate change in this fasciculation in the paralyzed muscle, showing that the twitching is not of spinal cord origin. However, when the nerve has been cut and allowed to degenerate, fasciculation no longer is seen in the denervated muscle following the administration of eserine. These facts strongly suggest that the effect of eserine may be to stimulate nerve activity, and to produce muscle twitching indirectly rather than by acting upon the muscle itself.

One the other hand, Eccles[4] in reviewing this problem, points out that eserine has little effect upon isolated nerve. The twitches produced by eserine are prevented by the administration of doses of curare much smaller than those required to block neuro-muscular conduction. If the impulses were originating in the nerve, one might expect that they would be stopped by curare only when neuro-muscular block was established. Eccles concludes from this that the effect both of curare and of eserine is at the myo-neural junction.

In view of the incompatability of these two opinions, it was felt advisable to search for evidence of motor nerve excitation by eserine in the intact animal. If eserine does stimulate the motor nerve, the impulse that proceeds distally to produce the fascicular twitch must also travel antidromically along the motor nerve and in the anterior root. Here, separated from sensory activity, these antidromic impulses should be demonstrable. It was to examine this possibility that the following experiments were carried out.

The experiments were performed on cats under chloralosane anesthesia, this drug having been selected because it is considered to have little effect

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upon neuro-muscular conduction[5]. Jugular and tracheal cannulae were inserted under ether anesthesia, after which the chloralosane was given intravenously in doses sufficient to keep the animals quiet without reducing reflex excitability. The usual dose was 150 mg. for a 2–3 kg. cat. A lumbar laminectomy was then performed, and the lower lumbar and sacral roots

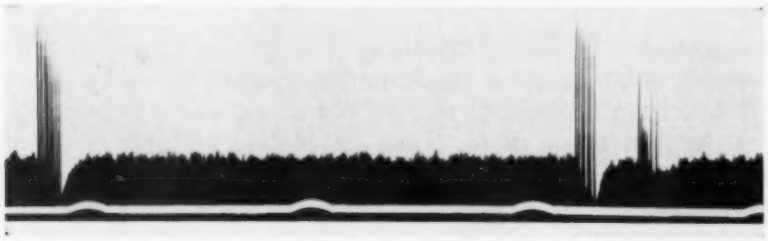

FIG. 1. Action potentials recorded from an anterior root of the cat following the administration of prostigmin, 0.25 mg. Time 0.3 sec.

were exposed within the spinal canal. The sensory roots were divided at a point near their entrance into the cord. The 5th lumbar and 1st sacral motor roots were isolated and sectioned near the cord in order to provide a long intra-spinal segment. With such a preparation it was possible to record from the anterior root, and to observe any impulses coming to it from the peripheral nerve. Action potentials were recorded by means of ringer-agar brush electrodes and a condenser-coupled amplifier.

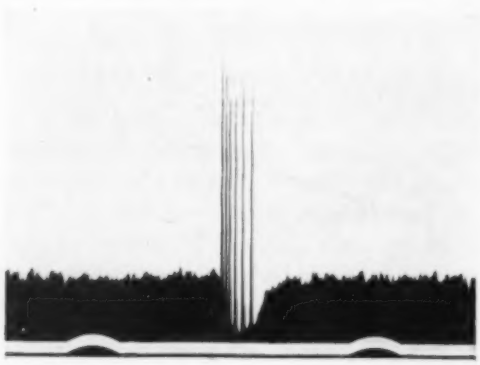

FIG. 2. Single burst of nerve impulses recorded from the anterior root of the cat following the administration of prostigmin, 0.25 mg.

With this preparation, no activity is normally observed in the anterior root. An occasional nerve exhibited spontaneous activity as a result of the trauma of the dissection, but rarely did this last for more than a few minutes. Following the administration of prostigmin, however, the nerve rapidly becomes active. Coincident with the appearance of fascicular twitching in the muscles (usually after intravenous doses of 0.2 to 0.7 mg. of prostigmin), there are observed rapid bursts of nerve impulses in the anterior root. The individual bursts may contain as many as twenty impulses, at a frequency of about 200 per sec. (Fig. 1 and 2). There is a close similarity between the activity recorded from the nerve and that which may be recorded from the muscles under similar circumstances (Fig. 3).

This similarity is also observed in another type of experiment. Following

the administration of prostigmin, it has been observed[6] that stimulation of a peripheral nerve causes a tetanic contraction of muscle rather than the usual twitch. It was therefore interesting to determine whether this repetitive response of muscle might also be associated with nerve activity. In order to do this, the sciatic nerve was freed in the thigh, and was sufficiently

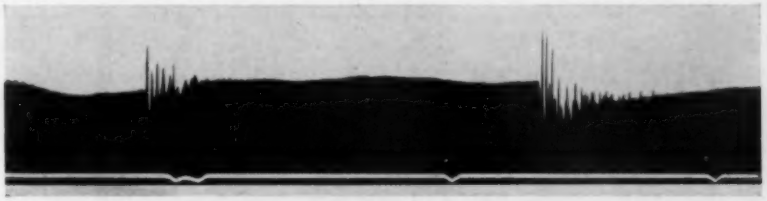

FIG. 3. Action potentials recorded from the gastrocnemius muscle of the cat following the administration of prostigmin, 0.25 mg. Record obtained with concentric needle electrode during active muscle fasciculation. Time 0.2 sec.

cleared to permit the application of silver electrodes for stimulation. Stimulation of the nerve in this way produces a strong contraction of the calf muscles, and at the same time a nerve volley is conducted up the nerve and may be recorded from the electrodes on the anterior root. After the administration of a small dose of prostigmin, this nerve volley recorded from the anterior root is followed by a short burst of random nerve impulses (Fig. 4). At the same time there is observed the well known repetitive response of the muscle. Following a short, high frequency tetanus, there is again a shower of nerve impulses in the anterior root, which under these circum-

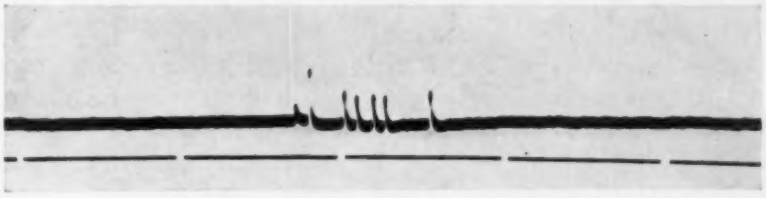

FIG. 4. Action potentials recorded from a few fibers of the anterior root of the cat during stimulation of the sciatic nerve after the administration of prostigmin, 0.25 mg. Time 0.05 sec. The small shock artifact is followed by the conducted impulse, after which there is repetitive activity in one nerve fiber.

stances may last more than a second. If one divides the sciatic nerve distal to the point of stimulation, or injects cocaine into it at this point, the directly conducted impulse remains unchanged, but the nerve activity after the volley is no longer observed. As one would expect, the muscle response is also abolished. It thus appears unlikely that this after-discharge could be the result of any local effect at the site of stimulation, and we must conclude that the repetitive stimulation of the nerve is occurring at a point somewhere near its distal end.

In order to prove that none of the nerve impulses were originating in the proximal portion of the nerve, an attempt was made to record impulses traveling down the nerve after the administration of prostigmin. To do this all the motor roots of the lumbo-sacral region were severed from the cord so that no normal motor activity would occur in the peripheral nerve. A small branch of the peroneal nerve, uncut, was then cleared, and recording electrodes were applied to it in the popliteal space. Under these conditions, one records a constant stream of sensory impulses traveling up the nerve. If, after the intravenous injection of prostigmin, the nerve is cut at a point distal to the recording electrodes, it is no longer possible to find any evidence of activity reaching these electrodes. One must conclude that the segment of motor and sensory nerve lying between the cut root within the spinal canal and the recording electrode in the popliteal space is not stimulated by prostigmin. The antidromic activity recorded from the anterior root must all originate in the terminal portion of the nerve.

If it is actually a portion of the nerve which is stimulated by prostigmin, one might expect that curare, which is thought to have its effect largely upon the myo-neural junction, might block the muscle response without affecting the nerve activity. This does not prove to be the case. In an animal showing active fasciculation as the result of prostigmin, the administration of curare results in prompt cessation not only of the muscle movement, but also of the nerve impulses in the anterior root. This occurs with small doses of curare insufficient to abolish indirect excitability of the muscle. In no instance did curare stop the visible twitching without also stopping the nerve activity, and in no instance did it stop the nerve activity without also stopping the muscle movement. As pointed out by Eccles[4], the rapidity with which the prostigmin effect is abolished by small doses of curare certainly suggests that the site of action of these two substances is the same.

The close association of nerve activity with movement suggested the possibility that the nerve activity might be the result of mechanical stimulation of the nerve endings by the muscle movement. Another possibility was that there are a few sensory fibers in the anterior root which carry impulses initiated by muscle movement. It was found, however, that stretching or pinching of the muscle did not result in any activity in the anterior root. In order further to examine this possibility, a slightly different preparation was used. A single motor root may be split longitudinally within the spinal canal in such a fashion as to produce two divisions of the root. These two divisions supply overlapping areas within the muscles which they innervate, and it is probable that the nerve fibers, intermingling distally, supply adjacent muscle fibers in many locations. It is thus possible to stimulate one division, and to record from another whose nerve fibers terminate within the muscle thus caused to contract. Under these conditions, following the administration of prostigmin, stimulation of one division does not produce any immediate "after-discharge" in the other. Following long continued stimulation of one division, there was observed on several occasions an in-

crease in the frequency of the bursts caused by prostigmin in the other. This, however, is a slowly developing phenomenon, and appears to differ from the immediate burst of activity which is observed when one stimulates and records from the same root. From these experiments it seems certain that muscle movement itself does not produce the nerve impulses recorded in the anterior root.

Results similar to those obtained with prostigmin were observed following the intra-arterial injection of acetylcholine. This injection was performed in the cat by the introduction of a small cannula into a branch of the popliteal artery. The solution to be tested was injected back through this branch into the popliteal artery. The muscle contraction which is observed following the injection by this technique of 0.1 mgm. of acetylcholine in 1.0 cc. of Ringer's solution is slow and irregular, and is associated with grossly visible fascicular movements of the muscle which persist for several seconds. Coincident with the muscle contraction, there appears a shower of antidromic impulses in the motor root supplying the area. The discharge differs slightly from that associated with the twitchings produced by prostigmin in that there is little tendency for the impulses to appear in bursts. Following the administration of curare (10 mgm.) it was found impossible to obtain either the muscle contraction or the nerve impulses by the injection of acetylcholine.

In this respect acetylcholine and prostigmin differ from certain other substances which are nerve stimulants. Although the intravenous injection of veratrine, guanidine, or tetraethyl ammonium chloride is followed by activity in the motor nerve, which may be recorded from the anterior root of the preparation described, this activity is continuous, does not occur in bursts, and is much more intense than that caused by prostigmin. In addition, it is unaffected by the administration of curare in amounts sufficient to stop the activity reflected in the muscles.

Discussion

The experiments cited above show that the appearance of fasciculation following the administration of prostigmin is associated with the occurrence of antidromic impulses in the anterior root, and that these impulses originate only in the region of the terminal portion of the nerve. The activity of the nerve is not the result of mechanical stimulation by muscle movement or contraction. It has also been demonstrated that acetylcholine is capable of producing similar nerve activity. Since prostigmin is known to lead to an accumulation of acetylcholine in muscle tissue[7,8], it is suggested that the stimulation observed following the administration of prostigmin may actually be due to the accumulation of acetylcholine which it produces.

In attempting to determine the site of action of the stimulating substance, several difficulties arise. If one assumes that the impulses are arising in the nerve at its ending, one is immediately faced with the fact that they cease following the administration of curare. This would mean that the ac-

tion of curare cannot be limited to muscle, but that it must also have an effect upon the nerve. If there is actually nerve stimulation by acetylcholine, it must be distinguished from the nerve excitation produced by guanidine, veratrine and tetraethyl ammonium chloride, which is unchanged following the administration of curare in doses much larger than those which completely stop any activity produced by prostigmin or acetylcholine. In other words, the action of curare and of acetylcholine on nerve is a peculiarly specific one, and is probably evidenced only at the nerve ending.

Furthermore, the action of acetylcholine is probably not limited to the nerve, for it has been shown to stimulate denervated muscle[9], possibly through an effect upon the motor end plate. Thus Harvey[10] observed that quinine prevents the stimulation of muscle by acetylcholine, but does not alter its stimulation by KCl. He suggests that KCl acts directly upon the muscle, whereas the acetylcholine might act upon the motor end plate. If this be its only site of action, one must assume that the impulse initiated by acetylcholine in the motor end plate is conducted not only to the muscle, but also antidromically into the motor nerve, and thus to the anterior root. In order to do this, the impulse would have to pass from end plate to nerve ending, and in view of the many experiments on neuro-muscular transmission which have led to the conclusion that conduction in this location is mediated by chemical agents, such a possibility seems extremely unlikely. It is much more likely that in the same way that acetylcholine stimulates the end plate, it also stimulates the motor nerve ending at the end plate.

In view of the above considerations, we are led to the conclusion that acetylcholine is capable of stimulating both muscle and nerve. This effect may be observed both when the drug is administered intra-arterially, or when it is caused to accumulate in the tissues by the administration of prostigmin. It is possible that the two effects are merely manifestations of the same action of the drug on similarly irritable structures. Whatever the details of this action may be, it would appear that the limited concept of a specific local effect of acetylcholine on muscle at the myo-neural junction is insufficient to explain the observation reported.

Summary

The fascicular twitching observed in animals following the administration of prostigmin is associated with antidromic nerve impulses which may be recorded from the anterior (motor) roots.

Both the fascicular twitching and the nerve impulses are abolished by small doses of curare.

Similar impulses are observed when a muscle is caused to contract by the intra-arterial injection of acetylcholine.

It is suggested that these experiments provide evidence that acetylcholine has a stimulatory effect not only on striated muscle, but on the terminal portions of the motor nerve as well.

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EFFECTS ON RESPIRATION, BLOOD PRESSURE AND GASTRIC MOTILITY OF STIMULATION OF ORBITAL SURFACE OF FRONTAL LOBE

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POSSIBLE autonomic functions of the orbital surface of the frontal lobe have been subjected to very little study. Spencer (1894) exposed this area in the cat, dog, rabbit and monkey, and found in all that slowing or arrest of respiration occurred most readily on stimulation of the "outer side of the olfactory tract just in front of the junction of the tract with the uncinate." In a larger area lateral, anterior and posterior to this the responses were similar but had a higher threshold. The nine tracings Spencer published to show stimulation in the cat and dog, all had as well a rise in blood pressure. He states that he found no circulatory changes from stimulation of this area in the monkey and his published tracings are in agreement therewith. W. K. Smith (1938) has found an area in the cat's gyrus orbitalis (gyrus compositus anterior) whose stimulation results in respiratory inhibition and a rise in blood pressure. He did not study the orbital surface of his monkeys. Recently Bailey and Bremer (1938) found that stimulation of the central end of the vagus nerve increases the electrical potentials of the orbital surface of the frontal lobe, and the present investigation follows up that finding.

METHOD

Adult domestic cats and monkeys (*Macaca mulatta*) were used in our experiments. The cats were anesthetized with 30–40 mg. per kg. of nembutal, the monkeys with 20–26 mg. per kg., followed by ether for operative exposure, if necessary. Using aseptic technique the orbital surface of the right frontal lobe was exposed by removing the contents of the orbit, its bony roof and the walls of the frontal sinus. The area on the orbital surface of the brain whose excitation produced respiratory arrest was then identified by stimulation with a bipolar copper electrode with the two poles 1 mm. apart and that area was next removed by subpial dissection. The wounds were closed by interrupted suture of anatomical layers. On the day the animal was to be sacrificed for histologic studies of the brain* it was anesthetized with ether, a tracheal cannula inserted, the left orbital surface exposed under light ether narcosis. In a few animals the tracings were made during stimulation of the right orbital surface. Respirations were recorded by means of a sphygmomanometer cuff around the thorax and abdomen attached to a tambour writing on a kymograph. With this apparatus the upstroke represents inspiration. The blood pressure in the common iliac artery (cannulated extraperitoneally) was recorded by a mercury manometer, and gastric movements were recorded by a water manometer connected to a stomach balloon inflated with 50–100 cc. of air. The stimulus was a 60-cycle sine wave alternating current obtained from the house lighting circuit and reduced to appropriate voltage (1–6 V).

RESULTS

From the portions of the gyrus orbitalis of cat and monkey indicated on the diagrams there were obtained: (i) slowing or arrest of respiration; (ii) a rise in blood pressure and (iii) a relaxation of the stomach.

* These studies will be communicated in a subsequent publication.

Respiration. Of these responses the respiratory inhibition had the lowest threshold, frequently appearing with a stimulus of 1 V in both cat and monkey. The features of the inhibition in cats described by Smith were in general corroborated by us. With a stimulus strong enough to stop the respiration this was the commonest sequence: a latent period of less than one second, cessation in full expiration for 5–10 sec., escape with slow shallow respirations, a deep breath after the stimulus ended, resumption of

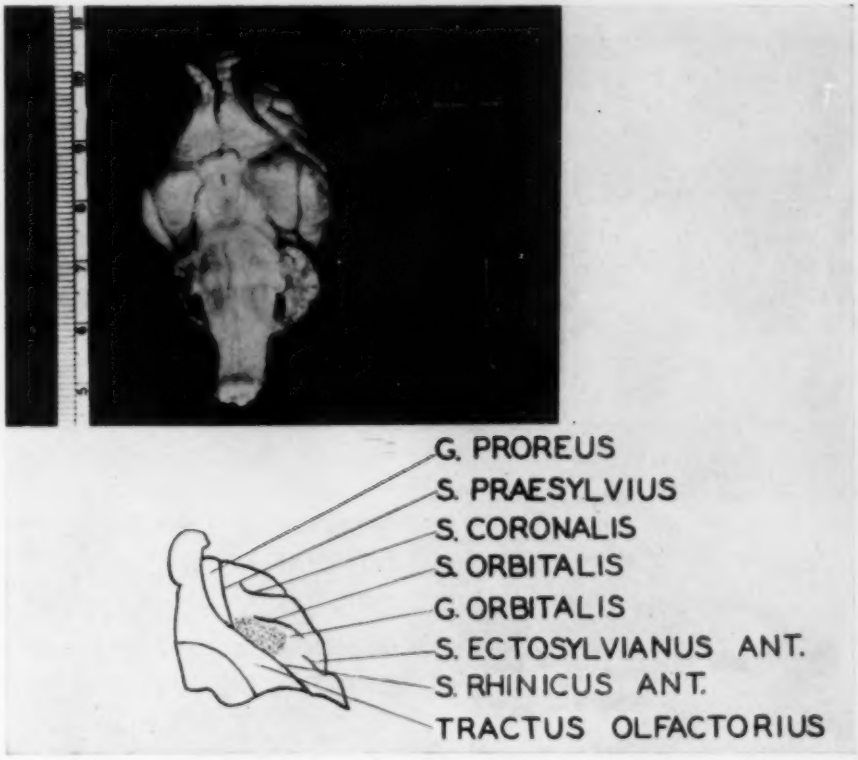

FIG. 1. Cat's brain—basal surface. Diagram below photograph shows orbital surface of left frontal lobe (×2). From the stippled area in gyrus orbitalis the described effects were obtained.

normal rate and amplitude at once. In the cats interruption also occurred and was maintained at any other phase of the respiratory cycle and some cats inspired slowly throughout the time of the stimulus. A few tracings show several nearly normal breaths after application of the stimulus before arrest appeared. Rarely escape from inhibition was shown by one deep breath followed by arrest again, or by a group of slow deep breaths continuing till the end of stimulation. Frequently there was no deep breath at the end of the stimulus. Rarely following stimulation a number of deep breaths intervened before the normal rhythm recurred; almost never did an

after-discharge of inhibitory effect succeed removal of the stimulus. When the voltage was inadequate to produce arrest the following varieties of inhibitory effect were seen: with decreased respiratory rate there might be either supernormal, normal or decreased amplitude; with unchanged respiratory rate the amplitude might decrease. Various combinations of the foregoing might occur during the application of a single stimulus. The maximum arrest obtained lasted 24 sec. following the application of 6 V. In one animal no respiratory inhibition could be produced.

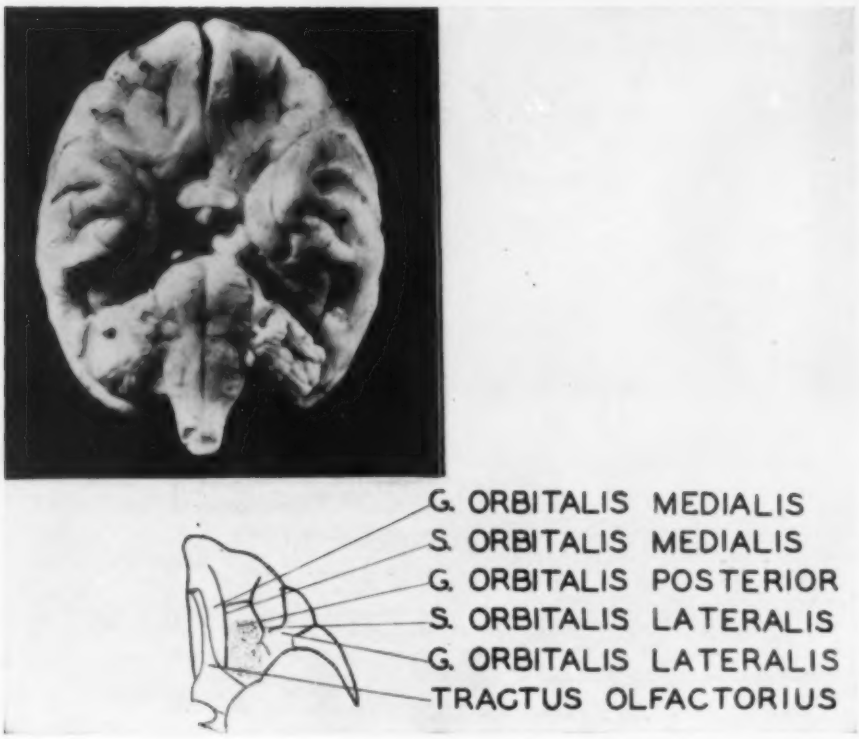

FIG. 2. Monkey's brain—basal surface. Diagram of orbital surface of left frontal lobe is natural size. Described effects were obtained from stippled area in gyrus orbitalis posterior.

Responses from the gyrus orbitalis posterior of the monkey corresponded to these in the cat except that: arrest never occurred in any phase but full expiration; there was frequently a shallow breath before full arrest; a deep breath at the end of stimulation was present more often; and respiratory inhibition occurred in each of the 6 monkeys stimulated.

Any inhibition obtained from the orbital surface outside the stippled area on the diagrams had a much higher threshold and did not occur regularly. In particular we found no inhibition following stimulation of the olfactory tract. Since the boundaries of the area shown depend for their

orientation upon the sulci, which vary from animal to animal, our diagram represents an approximation with a probable error of at least + or −1 mm. at any point on that boundary.

Blood pressure. The changes in blood pressure in the cats were typically as follows: 2–7 sec. after application of the stimulus there was a gradual rise in blood pressure, which continued until the end of a 10–25 sec. stimulus, and was succeeded by a more rapid fall to the original level. The increases were nearly always less than 10 mm., and there was rarely an unequivocal rise in blood pressure unless the stimulus were sufficiently strong to halt the respiration. Three of 10 cats gave no rises in blood pressure at all, although respiratory arrest was obtained in them. In the other 7 cats about 20 per cent of the stimuli producing respiratory standstill caused no certain change in the blood pressure. Since all of the animals in this series had pressures below 70 mm. Hg by the time the extensive operative preparation was completed a part of the failure of response may have been due to shock. The responsiveness of the cortex was usually greater an hour after the exposure than immediately thereafter. Variations in the details of the response were numerous. At times the stimulus was followed by a drop of 2–3 mm. in pressure before the rise occurred; at times the rise began with a latent period of less than 1 sec. or greater than 7 sec.; occasionally during the recovery phase there was a dip below the original level before it was resumed.

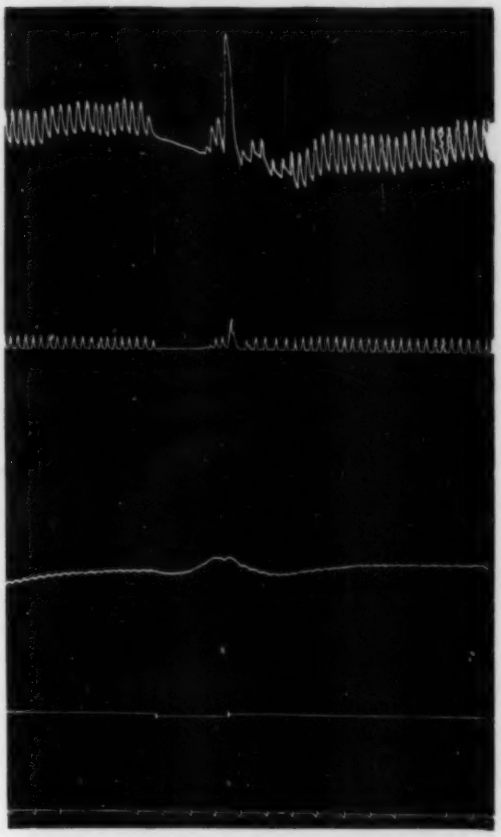

FIG. 3. Monkey No. 3. Top tracing—intragastric pressure; second tracing—respiration; third tracing—pressure in common iliac artery; fourth tracing—signal marker for stimulus; fifth tracing—time at 5 sec. intervals.

Stimulus 6 V applied to stippled area shown in Fig. 2. Respiratory excursions superimposed on the level of gastric tonus in first tracing. Maximum gastric relaxation 15 sec. after stimulus off with gradual return toward the pre-stimulation level. After onset of stimulus one respiration at half normal amplitude before the complete arrest. Slight drop and then a rise in blood pressure.

In the monkey the rises in blood pressure were obtained more consistently, were higher, and were often present when the respiration was merely

slowed. In each of the monkeys in which respiratory arrest was obtained, elevations of blood pressure of 10–20 mm. occurred at least once during stimulation and in one macaque the rise averaged 14 mm. for all stimuli arresting respiration. The average detailed behavior of the changes in arterial pressure corresponded to those in the cats and this average was subject to the same variations. In areas outside the stippled region shown on the diagrams rises in blood pressure of more than 2–3 mm. were not obtained from the orbital surface of the frontal lobe in either cat or monkey.

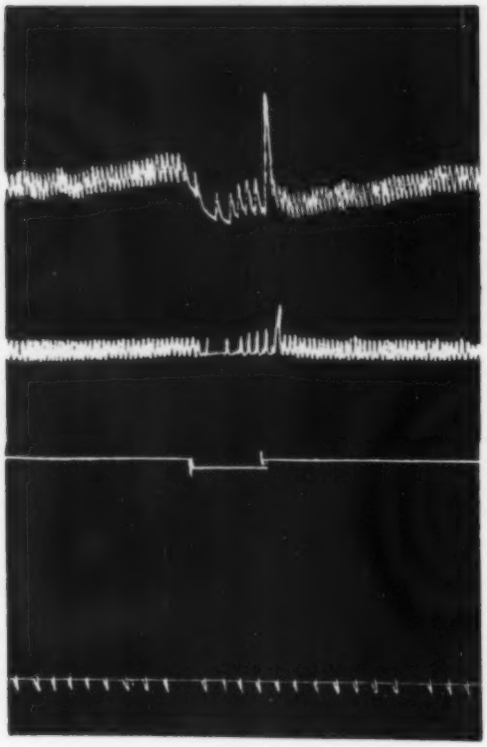

FIG. 4. Monkey No. 1. Tracings same as Fig. 3 except for absence of blood pressure curve. Stimulus 3 V applied to area shown in Fig. 2. Abrupt decrease in tonus of gastric muscle although no prolonged respiratory arrest appeared. In both Fig. 3 and 4 the prominent spike in the first and second tracings represents the deep breath appearing immediately upon cessation of stimulus.

Tonus of gastric muscle. In the state of light narcosis in which the animals were held during stimulation, the gastric wall containing an inflated balloon either maintained a relatively constant state of tonus or exhibited rhythmic fluctuations of contraction and relaxation. Sudden marked spontaneous alterations of tonus were not observed. Sharp relaxations took place, however, upon stimulation.

In the cats such relaxation occurred in only 20 per cent of the stimulations of the appropriate area, and in 3 of 10 cats no relaxation of the stomach took place following any stimulation. In monkeys, however, the responses were clearcut and consistent. Typically there occurred within one second of the onset of the stimulus a brisk diminution of tonus in the gastric muscles, the curve sloping off to a maximum fall 5–25 sec. after a 10–20 sec. stimulus and gradually returning to near the previous level during 10–80 sec. A latent period of several seconds before the relaxation began, and a partial or no immediate recovery of the tonus were the chief variations noted. Over 95 per cent of the stimuli which stopped respiration were accompanied by gastric relaxation, and 90 per cent of the positive responses of the stomach were so prompt and brisk that they were unquestionably due to the stimulus. Frequently the gastric tonus decreased with stimuli only sufficient to

slow and not stop the respiration, and infrequently gastric relaxation occurred at an even lower threshold than that for any inhibitory effect on respiration. Since the onsets of dilatation and subsequent contraction of the stomach were at times exactly coincidental with cessation and resumption respectively of the respiration, the possiblity of the gastric responses being due to a mechanical artifact from absence of the inspiratory pressure of the diaphragm was considered. The facts that respiratory arrest also occurred with no change in the gastric volume, that relaxation of the gastric muscle occurred at times with stimuli which caused no respiratory change, that occasionally abrupt gastric relaxation occurred with a shorter latent period than that for respiratory alteration and that gastric volume usually returned to its previous level slowly in the manner of smooth-muscle contraction rather than promptly with the resumption of normal respiration, led us to conclude that the mechanical factor was at most a minor one in explaining the shifts in the curves of gastric response.

Accessory effects. The masticatory, glossal and deglutitory movements noted by W. K. Smith in his cats upon stimulation of the area inhibiting respiration were seen also by us. These movements occur in less than one-half of the stimuli inhibiting respiration, and we agree that they are more likely to occur when the anterior part of this area is stimulated. We also noted that stimulation of the gyrus orbitalis immediately adjoining the horizontal ramus of the sylvian fissure occasionally caused closure of the contralateral eye. None of these phenomena occurred during stimulation of the gyrus orbitalis in the monkey.

Summary

From the orbital surface of the frontal lobe in both cats and monkeys an area in the gyrus orbitalis near the olfactory tract was found to give rise upon stimuli of 1–6 V to inhibition of respiration, rise of blood pressure and decrease in the tonus of the gastric musculature. The respiratory effect was obtained nearly always in the cat and always in the monkey; the elevations of arterial pressure were higher and more consistently present in the monkey; the inhibition of tonus in the gastric muscles occurred only infrequently in the cat but in the great majority of instances in the monkey.

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